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GANGLIOGLIOMA

TUMOR OF THE CENTRAL NERVOUS SYSTEM; REVIEW OF THE LITERATURE AND REPORT OF TWO CASES*

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Since some semblance of order was brought out of the existing confusion by Virchow [1] in his classification of tumors composed of nerve elements, many contributions to the study of their pathology have been made. Of this fairly replete literature no small portion has been devoted to the class of tumors, not without their peculiar interest, that are derived from the undifferentiated and differentiated cellular elements. In this group the commonly termed ganglioneuroma has occupied an important place, and a fairly large series of cases has been reported.

In 1870, Loretz [2] reported the first authentic case in which the tumor was found in the left thoracic cavity in the angle between the second and third dorsal vertebrae and the ribs. Since that time, sixty odd cases occurring in various parts of the nervous system have been added to the list. Of these a comparatively small number were located in the brain and spinal cord. Dunn,[3] in his review of the literature, classified these tumors from the standpoint of their anatomic position as follows: (1) those originating in the sympathetic nervous system: (*a*) cervical segment, (*b*) thoracic segment, (*c*) abdominal segment of chain and branches, (*d*) suprarenal, (*e*) that of the subcutaneous tissues; (2) those originating from the peripheral nerves; (3) those originating in the central nervous system.

While there are several references to this class of tumors situated in the central nervous system, none of the recent contributors has seen best to review the entire literature on the subject. It is the purpose of this study to give a summary of the clinical and anatomic observations in all reported cases as well as to describe two others that I have had the opportunity to study.

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1. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1864, vol. 2, p. 150.

2. Loretz, W.: Ein Fall von gangliosem Neurom (Gangliom), Virchows Arch. f. path. Anat. **49**:435, 1870.

3. Dunn, John S.: Neuroblastoma and Ganglioneuroma of the Suprarenal Body, J. Path. & Bact. **19**:456 (July) 1914-1915.

TERMINOLOGY

Because of the confused state of the nomenclature applied to this tumor, it is well to review briefly some of the essential features of the terminology of tumors. The general rule for applying a name to a new growth is that it should describe either its etiology, its regional location, its histologic structure or, preferably, its histogenesis.[4] The last principle suggests the type of cell or cells of the growth and probably serves best by indicating the chief characteristics of its component elements. Virchow, in the aforementioned classification of the neuromas, gave the name "neuroma gangliocellulare" to neoplasms containing new-formed ganglion cells. Since that time many other terms have been used, such as ganglionic neuroma, neuroganglioma, neuroglioma, ganglioneuroma, ganglioglioneuroma and ganglionic glioma. In most of these names the idea of the presence of ganglion cells is indicated and in others, applied after a more complete knowledge of the structure of the tumor was ascertained, the occurrence of glial elements was signified. The complicating feature lies in the use of the term "neuroma," which denotes the presence of nerve fibers. Found in great numbers in this tumor, they are considered by all recent investigators to be the product of the nerve cell. If one is to include the products of the constituent cells, one must include also those of the glial elements, for such are present and have a part in the neoplastic elaboration of the structure. Any such term would obviously be bunglesome and therefore impractical. It must be said that the term "ganglioneuroma" has the advantage of common use, especially by English and American contributors, although evidently it is inaccurate in that it names only one of the cellular constituents of the tumor. German writers use the name "ganglioglioneuroma" to qualify this particular tumor. A more appropriate and a simple name would be ganglioglioma,[5] in which the two essential constituent cells are indicated. This could be applied, however, only to those tumors which are found in the central nervous system and which contain true developing glial elements. Another name, ganglioneurinoma, indicating the presence of the sheath cells of Schwann, counterparts of the glia cells, would necessarily have to be applied to the tumors associated with the sympathetic nervous system.

4. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 26.

5. The name ganglioglioma was first suggested by Ewing and used by Perkins in the description of his case. In his book, however, Ewing seems to favor the term ganglionic glioma (footnote 4, p. 440). In this article I shall use the term ganglioglioma in all instances except in the previously reported cases, when the term used by its contributor will be given.

EMBRYOLOGIC CONSIDERATIONS

Whatever new information future study may yield as to the essential cause of tumors in general, it cannot be denied that there is a definite relationship between the histogenesis of the central nervous system and growths of a neoplastic type arising within its tissues. This seems to be definitely established in tumors of the glioma group wherein cell types of the developing glia elements have been demonstrated by specific staining methods. This is especially true of that type of glioma, the medulloblastoma, which occurs in the midline of the cerebellum in childhood, probably having its origin in the undifferentiated cells in the roof of the fourth ventricle.[6] In a similar manner, Cushing[7] indicated the probable relationship between the commonly called dural endotheliomas and the small clumps of cells in the arachnoid, the meningocytes, and he has therefore applied the term meningioma to the tumor.

In the type of tumors under consideration, there is also an obvious relationship between its constituent cells and those found in the embryonic nervous system. Neoplasms of a malignant nature composed of neuroblasts and sympathoblasts are found not infrequently and are described in the literature. In those of a more benign character, such as the ganglioglioma, the cells become more completely differentiated and the adult forms are a conspicuous element in its structure. Occasionally, those composed of both undifferentiated and differentiated elements are observed in which the less developed portions have a malignant nature, being capable of metastasizing to other locations.[8] A transformation of a malignant sympathicoblastoma into a benign ganglioneuroma has recently been studied and reported.[9] In the series of tumors which have been collected from the literature as well as in the cases studied personally, the occurrence of embryonic cell types as well as adult cells has been noted. In view of this fact a brief

6. Bailey, Percival, and Cushing, Harvey: Medulloblastoma Cerebelli: A Common Type of Midcerebellar Glioma of Childhood, Arch. Neurol. & Psychiat. **14**:219 (Aug.) 1925.

7. Cushing, Harvey: Studies in Intracranial Physiology and Surgery: The Third Circulation and Its Channels, London, Oxford University Press, 1926, p. 41.

8. Beneke, Rudolf: Zwei Fälle von Ganglioneurom, Beitr. z. path. Anat. **30**: 1, 1901. Jacobsthal, E.: Ganglioneuroma des Ganglion Coeliacum, Verhandl. d. deutsch. path. Gesellsch. **13**:343, 1909. Miller, John W.: Ein Fall von metastasierenden Ganglioneurom, Virchows Arch. f. path. Anat. **191**:411, 1908. Wahl, H. R.: Neuroblastoma: With a Study of a Case Illustrating the Three Types That Arise from the Sympathetic System, J. M. Research **30**:205 (May) 1914. Dunn (footnote 3).

9. Cushing, Harvey, and Wolbach, S. Burt: The Transformation of a Malignant Paravertebral Sympathicoblastoma into a Benign Ganglioneuroma, Am. J. Path. **3**:203 (May) 1927.

survey of the features of the histogenesis of the nervous system seems advisable at this point.

HISTOGENESIS OF THE CENTRAL NERVOUS SYSTEM

It is from the germinal cell in the original neuro-epithelium that most of the cells in the adult nervous system have their origin (microglia are probably exceptions). These cells give rise to the ependymal and the indifferent cells, the latter being termed medulloblasts by Bailey and Cushing. The indifferent cells are essentially bipotential and are capable of giving rise to daughter cells which develop into either ganglion cells or glia cells, passing through more or less characteristic stages in either case.

The Neuron Series.—The earliest type of cell is the apolar neuroblast which is globular, with the cytoplasm collected toward one pole of the cell. The cytoplasm has a special affinity for reduced silver, this characteristic being utilized in the recognition of the cells in the group. With the rapid increase in the amount of cytoplasm, two processes develop at opposite poles of the cell (bipolar stage). One of the two is soon absorbed (or the two are fused), so that a unipolar pyriform cell is formed, the single slender process being the future axon of the cell. This is the "neuroblast stage" of His, but for the sake of uniformity it has been given the name unipolar neuroblast. The nucleus increases in size and becomes vesicular by the collection of the chromatin material into one or two darkly staining nucleoli. The stage of the multipolar neuroblast is reached when other processes are protruded, the cell assuming an irregular stellate shape. Differentiation is completed when the network of neurofibrils is formed in the cytoplasm and basophilic granules are deposited in its meshes.

This brief description of the development of the ganglion cell applies particularly to the cells lying within the central nervous system. The cells which come to be situated in the ganglionic masses attached to the peripheral nerves and the sympathetic system undergo the same developmental changes, except that the end-cell may vary in shape from the typical multipolar neuron. The dorsal root ganglion cell is unipolar or bipolar (the latter occurring in the ganglion of the nervus acusticus), the cells probably not passing through the multipolar stage in the developmental process. Those in the sympathetic ganglia are chiefly multipolar, although some are found to be bipolar and unipolar.[10]

The essential difference in the development of the ganglion cells in the neuraxis and those situated in the peripheral ganglia is the migration of the latter to points at variable distances from their origin in the

10. Ranson, Stephen W.: The Anatomy of the Nervous System, ed. 3, Philadelphia, W. B. Saunders Company, 1927, p. 343.

neural crest. This process of migration probably explains the more frequent occurrence of the tumor in the sympathetic nervous system as compared with that in the central nervous system. Any interference with the progress of the cell, so that it is arrested in its course or so that it comes to lie in an abnormal situation, will probably result in "cell rests," which, according to the cell inclusion theory of Cohnheim, are potential tumors. It is not unreasonable to believe that ganglioneurinomas of the sympathetic system have their origin in this manner.

Neuroglia Series.—The earliest cell of this series makes its appearance as a primitive spongioblast, which, according to some investigators, is a step between the ependymoblast and the bipolar spongioblast. The latter differs from the bipolar neuroblast only by a specific affinity of its cytoplasm for gold sublimate and perhaps by a larger number of chromatic granules in its nucleus. The development of numerous processes, one of which becomes attached to a blood vessel, characterizes the astroblast stage. At this time the cell assumes a stellate shape, due to the molding of the cytoplasm of the cell by surrounding nerve fibers or nerve cells. The astrocyte develops by minor changes in the cell body and an increase in the number of processes. If it is a fibrillary astrocyte, the characteristic neuroglia fibrils, probably elaborated by the protoplasm, are found passing through the cell body and extending from its processes. The protoplasmic astrocyte is distinguished by the absence of fibrils and the presence of gliosomes, which are granules probably of the nature of mitochondria.

With this brief summary of the histogenesis of the nervous elements in mind, a review of the cases of gangliogliomas can be undertaken to better advantage, especially from the point of view of their histologic constituents.

REPORTED CASES OF GANGLIOGLIOMA [11]

CASE 1 (Worcester [12]).—*Neuroglioma of the left parietal region.*

Clinical History.—A grocer, aged 42, began to fail mentally and physically two years previous to admittance to a hospital for mentally defective patients. He became dull and listless, later developing a definite speech defect. His gait became unsteady and his handwriting illegible.

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11. The case of H. Haenel is not included in this series. He found two small tumors in the region of the right orbital fissure attached to the dura mater, which, on histologic examination, were found to contain ganglion cells and myelinated nerve fibers (Beitrag zur Lehre von den aus Nevengewebe bestehenden Geschwülsten, Neuroganglioma myelinicum verum, Arch. f. Psychiat. **31**:491, 1899). In this study I am concerned with tumors arising within the tissues of the central nervous system proper and shall not consider those arising from the membranes or cranial nerves.

12. Worcester, W. L.: New Formation of Nerve Cells in a Cerebral Tumor—Neuroglioma, J. M. Research **6**:59, 1901.

Physical Examination.—In addition to the symptoms detailed, the patient presented a slight right hemianesthesia and a very marked right-sided astereognosis. The optic disks appeared slightly hyperemic, and this became more pronounced during the course of the illness. The mental sluggishness and physical weakness were progressive and were associated with attacks of nausea and convulsions on several occasions. The patient died about a year after his admittance.

Gross Pathology.—At necropsy a large cyst was found in the left parietal region of the brain with very thin walls separating it from the lateral ventricle and the cortex. Projecting into the cyst from its lateral wall was a firm nodule or tumor about 2.5 cm. in diameter which in turn contained several small cysts.

Histopathology.—The tumor extended externally as far as the pia mater. In this region considerable connective tissue was found which decreased in amount as the interior of the tumor was approached, where it was chiefly confined to the walls of the blood vessels.

The cellular elements consisted of neuroglia, essentially of the adult type, and morphologically characteristic ganglion cells. The latter were chiefly multipolar and were more or less pyramidal in shape. The nuclei, frequently multiple, were lightly stained and contained a dark nucleolus. Typical granulation of the protoplasm as found in the cortical ganglion cells was not observed. A third cellular element containing one or more nuclei and fairly large was found at the margin of the tumor. The cells were spherical and were considered to have a phagocytic function.

Comment.—This is probably the first case of true ganglioglioma to be reported. The value of the contribution would have been greatly enhanced if the nature of the stroma had been investigated with specific methods. The gliomatous nature of the smaller cells would undoubtedly have been established. The presence of the large cyst associated with the tumor should be noted; in this respect it resembles several of the other cases. In situation the new growth compares with that reported by Dumas.

Case 2 (Dumas [13]).—*Neuroglioma ganglionare of the right cerebral hemisphere.*

Clinical History.—A woman, aged 29, had suffered with severe headaches for a year; preceding death she had complained of dizziness and vomiting.

Gross Pathology.—The details supplied in the contribution are extremely meager, probably owing to the fact that the author was dependent on another physician for the information. "The tumor is of the size of a cherry, of a soft consistency and white color, taken from a woman 29 years of age. Section of the brain, according to the physician who sent the tumor to the Pathological Institute, showed a dilatation of the right ventricle. Its wall in the posterior inferior portion was as thin as paper and perforated in one place. In this situation was the tumor."

Histopathology.—Section of the tumor revealed a connective tissue stroma, arranged in fibrous bands, and surrounding parenchymatous areas composed of cells and fine fibrillary material. The conspicuous elements, in groups or scattered thoughout the tissue, were large multiform cells with one or more large vesicular nuclei, each containing a spherical nucleolus. The protoplasm, while somewhat

13. Dumas, Alexander: Ueber einen Fall von Neuroglioma Ganglionare des Grosshirns, Inaug. Diss., Würzburg, 1904.

granular, failed to show typical Nissl's substance with the methylene blue (methylthionine chloride, U. S. P.) stain. One or more processes were observed which could be traced for some distance in the network.

Glia cells and fibers were definitely demonstrated by Mallory's stain. The author referred also to groups of round lymphocyte-like cells about the blood vessels. In addition to these were "small round cells which by their morphology remind one of the so-called glia granules ('Gliakörner') as found very frequently in the white substance of the brain. Besides these small glia cells with spherical, darkly staining nuclei, we find spindle-shaped cells which, when observed singly, show marked and abundant glia processes which usually arise from the poles of the spindle cells. They are therefore spindle-shaped glia cells."

The network of the parenchymatous portion of the tumor was composed of fibers which had the morphology of glia fibers, axis cylinders and process of protoplasmic character arising from the ganglion cells, as previously mentioned. With the myelin stain the author demonstrated fine myelinated fibers throughout the tumor structure.

"Concluding our investigations there is no doubt but that we are dealing with a tumor of nervous tissue which consisted of ganglion cells, myelinated as well as unmyelinated nerve fibers in addition to supporting elements. The fact that in the nervous constituents of the tumor we are dealing with elements of new growth and not with pre-existing nervous structures which by the growth of the tumor have been included in its substance, is proven by the fact that the tumor is not an infiltrating neoplasm but an expansively growing spherical mass extending in the cavity of the right lateral ventricle. We therefore are entitled to name the tumor neuroglioma ganglionare."

Comment.—This case is not usually included in the lists of cases of ganglioglioma as reported by some writers.[14] Dumas fell into the error of confusing the cases of Baumann[15] and Hartdegen[16] with true tumors, for these are without doubt heterotopic manifestations and are so considered by their contemporary (Schmincke). The facts, however, that the growth is not cortical but located in the medullary substance in the region of the occipital lobe and extending into the ventricle, that the description of the microscopic appearance corresponds so closely with that of other observers and finally that the work was done under the direction of Borst and von Rindfleisch who had reported accepted cases of this tumor two years previously,[17] seem to be conclusive evidence that this was a true ganglioglioma.

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14. Dunn (footnote 3). Wahl (footnote 8, fourth reference).

15. Baumann, G.: Beitrag zur Kenntnis der Gliome und Neurogliome, Inaug. Diss., Tübingen, 1877; Zeigler's Beiträge, 1887, vol. *2*; quoted by Dumas (footnote 13); quoted by Schimincke: Verhandl. d. deutsch. path. Gesellsch. **17**:537, 1914.

16. Hartdegen: Ein Fall von multipler Verhartung des Grosshirns nebst histologisch eigenartigen harten Geschwülsten der Seitenventrikel, Arch. f. Psychiat., 1881, vol. 11; quoted by Dumas (footnote 13); quoted by Schmincke: Verhandl. d. deutsch. path. Gesellsch. **17**:537, 1914.

17. Borst, Max: Die Lehre von der Geschwülsten, Wiesbaden, J. F. Bergmann, 1902, p. 242. Von Rindfleisch, cited by Borst.

CASE 3 (Schmincke [18]).—*Ganglioneuroma of the right temporal lobe.*

Clinical History.—A boy, aged 17, began to have epileptic seizures at the age of 8, which continued throughout the period of his illness. He later became idiotic and was confined to an asylum, where he died in a convulsion.

Gross Pathology.—An egg-shaped tumor, about the size of a walnut, was found embedded in the white substance of the anterior part of the right temporal lobe. It was of firm consistency and grayish white, and appeared somewhat granular on cross section. It was easily separable from the normal brain tissue. As a matter of interest, the brain was larger than normal, weighing about 1,580 Gm.

Histopathology.—The tumor was composed of a fibrous stroma in which were situated cells of various types. This stroma consisted of connective tissue fibers that had their origin in the wall of the blood vessels, together with definite glia and nerve fibers as demonstrated with special stains. The network surrounded alveolar-like spaces that contained groups of cells, although some were scattered through the denser portions of the tissue.

Of the cellular elements, those having the characteristics of ganglion cells were the most prominent. They were unipolar or multipolar and frequently multinucleated, undergoing amitotic cell division. The large and vesicular nuclei contained each a large spherical nucleolus. The cytoplasm had a granular appearance, although typical Nissl's granules were not observed. The Weigert myelin stain demonstrated granules in the cytoplasm, indicating a degeneration process similar to that mentioned by other observers. The protoplasm of these cells also contained typical neurofibrils.

Other cells, about the size of lymphocytes or even larger, were found in groups especially about the blood vessels. These "Bildungsnester" or "Proliferationzentren" were considered by the author to be situations where the differentiation of the ganglion cells and the glia cells took place. This conclusion was drawn from the morphologic characteristics of the cells rather than from their reaction to specific stains. Long rows of cells were also found which, at the time, the author considered to be the formative elements for the many nerve fibers in the tumor.

While Schmincke mentioned the presence of glia fibers in a definite way and placed considerable emphasis on the occurrence of the developing neuroglial elements, he did not lay much stress on the occurrence of adult glia cells. The tumor was richly supplied with blood vessels the structure of which corresponded to that of capillaries, veins and arteries.

Comment.—This case of Schmincke is of interest in that it was associated with megalencephaly of a definite character; this relationship is stressed in this contribution as evidence of the congenital origin of this type of tumor. Another feature is his conception of the origin of the multitude of nerve fibers in the tumor, i. e., from the rows of cells. This was fairly conclusively refuted in the paper by Pick and Bielschowsky and one finds that Schmincke himself, in reporting his second case, was ready to abandon the idea.

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18. Schmincke, Alexander: Beitrag zur Lehre der Ganglioneurome: Ein Ganglioneurom des Gehirns, Beitr. z. path. Anat. **47**:354, 1909-1910.

CASE 4 (Pick and Bielschowsky [19]).—*Ganglioneuroma of the upper part of the cervical cord and the medulla oblongata.*

Clinical History.—A woman, aged 24, was brought to the City Hospital in Friedrichshafen with symptoms of active tuberculosis of the lungs. She presented a single symptom which indicated a disturbance of the nervous system: hiccups which occurred at the rate of two or three a minute during her waking hours.

Physical Examination.—The patient was weak and cachectic and had persistent hiccup. There were cavities in the upper lobes of both lungs. With the exception of contractures of the fingers of both hands, there were no noticeable abnormalities of the motor system.

Tactile sensibility was unimpaired; other modalities were not tested. The skin and tendon reflexes were normal. There were scars on both hands where a supernumerary digit had been removed, and one foot had six toes.

Gross Pathology.—The usual changes of advanced tuberculosis of the lungs were present. In addition to the pathologic changes in the lungs, there were a parenchymatous degeneration of the heart muscle and both kidneys and tuberculous ulcerations of the intestine.

Entirely unsuspected, a tumor was found involving the posterior funiculus of the cervical spinal cord and medulla. It extended from the second cervical segment up through the medulla and probably into the pons for some distance, being confined to the right side of the organ where it resulted in marked bulging.

On cross section the tumor appeared brownish and was distinguished by its firm consistency from the surrounding central tissue, from which it was sharply demarcated. Figure 1 shows the tumor in a section of the first cervical segment in which it filled the right posterior funiculus almost completely. The left posterior funiculus and surrounding region showed areas of degeneration which were caused by the pressure of the tumor. The area indicated by *G* indicates a conglomeration of new-formed vessels and fibrillary connective tissue streaks which have their origin in the adventitia of the vessels. The pia in this region is markedly thickened.

Histopathology.—The tumor was characterized "as a stroma consisting of a very vascular, glious network in which numerous unmyelinated nerve fibers and ganglion cells were embedded." In the tumor there were areas of both loose and dense structure. In the former, the glia fibers had no definite arrangement, while in the latter they were in parallel bundles. Adult astrocytes were present, together with some lymphocyte-like cells, probably their progenitors. In some areas the adult cells were fused together to form a syncytium. Some of the glia cells were loaded with products of degeneration.

In the looser zones of the tumor were many ganglion cells, which were spherical, pyramidal, spindle-shaped or multipolar. These cells demonstrated all the characteristics of typical ganglion cells, having a vesicular nucleus containing a single globoid nucleolus, Nissl's substance and neurofibrils, as well as dendrites and axons. No mitotic figures were observed, but multinucleated forms and dumbbell-shaped nuclei indicated complete or incomplete amitotic cell division. The ganglion cells were found to undergo degeneration of various types, especially lipoidal (fatty degeneration) in the form of large and small globules, the formation

19. Pick, Ludvig, and Bielschowsky, Max: Ueber das System der Neurome und Beobachtung an einem Ganglioneurom des Gehirns nebst Untersuchung über die Genese der Nervenfasern in "Neurinomen," Ztschr. f. d. ges. Neurol. u. Psychiat. **6**:391, 1911.

of vacuoles, and finally the formation of small knotlike masses which, according to Bielschowsky, arise from the relations between the disintegrating protoplasm of the ganglion cells and the accompanying glia cells.

A rich network of unmyelinated nerve fibers was found in the tumor, either in a tangled mass or arranged in parallel bundles, much like those of glial origin. The fibers tended to form pericellular networks about the nests of the ganglion cells. The authors stated that one of the peculiarities of these fibers is their tendency to branch, some of which terminate in small spherical endings, resembling "glitter balls." In this case they tended to infiltrate the surrounding normal tissue. A few degenerating myelinated fibers were found and were considered to be accidental inclusions of longitudinally coursing fibers in the new growth.

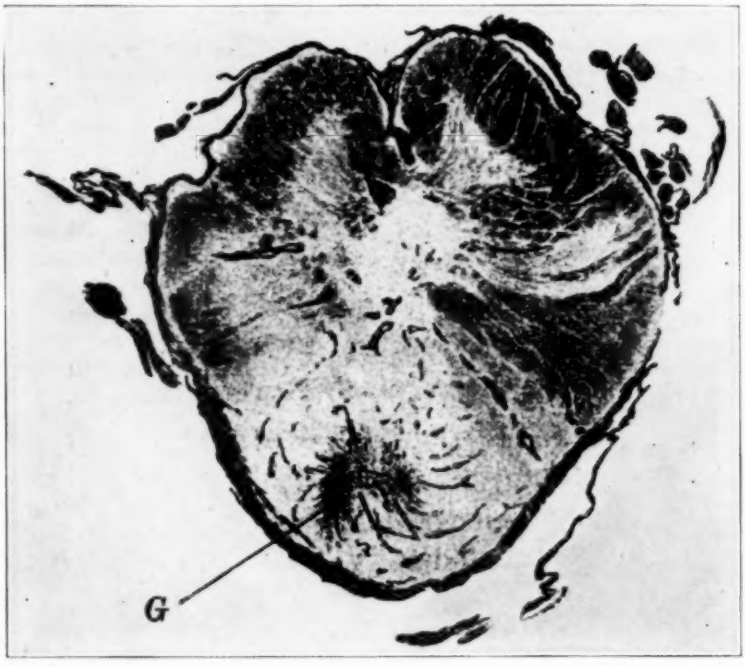

Fig. 1 (case 4).—Ganglioglioneuroma of the cervical cord. *G* indicates a mass of new-formed blood vessels with connective tissue derived from their walls. (After Pick and Bielschowsky.)

The small lymphocyte-like cells were considered as undifferentiated bipotential cells which were capable of forming either glia or ganglion cells. They were often grouped in masses, the so-called "developing nests."

Comment.—This case presents several points of special interest. The authors called attention to the supernumerary digits and suggested a possible relation between this anomaly and that of this somewhat rare tumor. The rather extensive growth in the cervical cord and medulla was entirely unsuspected, the pulmonary disease occupying the center of the clinical picture. The only symptom that might have sug-

gested involvement of the central nervous system was the persistent hiccup, probably due to phrenic disturbance. In view of the location of the tumor, the patient must certainly have had a loss of proprioceptive sense on the side of the lesion and probably also on the opposite side due to the destruction of the adjacent tissue by pressure.

This case is also singular in that it is the only case of ganglioglioma of the spinal cord, and is truly a pathologic rarity. Its origin can at best be only a conjecture.

CASE 5 (Achucarro [20]).—*Ganglioneuroma of the cerebellum.*

Clinical History.—A cartwright, aged 20, gave a history of falling from a horse which resulted in momentary unconsciousness. The onset of the present illness occurred shortly afterward with dizziness, recurrent vomiting and severe headaches of fronto-occipital type. After a short while he became blind and staggered when he tried to walk.

Physical Examination.—The patient, totally blind, showed definite disturbance in equilibrium, walking with a wide base. He was dizzy when standing but did not fall. Bilateral papilledema was present; the pupils did not react to light. In the occipital region there was marked pain, which was exaggerated by percussion. The patellar reflex was increased on both sides; Babinski's sign was absent, and the left abdominal and cremasteric reflexes were diminished. Babinski's sign of cerebellar asynergy was present.

The patient died six hours after a negative suboccipital exploration.

Gross Pathology.—The tumor was found in the cerebellum in the region normally occupied by the uvula and the tonsils (fig. 2). It was somewhat firm in structure and in section was from 4 to 5 cm. in diameter. "The tumor itself consisted of two parts, a gray firm mass on the right side which was connected with the olive, and another, a large cystic cavity on the left side, was apparently partly connected with the ventricle and partly separated from it by a thin wall."

Histopathology.—The firm portion of the tumor was composed of cellular elements embedded in a stroma, a large part of which consisted of connective tissue septums which had their origin in the adventitia of the blood vessels. The most conspicuous type of cell was the ganglion cell which showed evidences of progressive variations from the normal. They contained one or more large vesicular nuclei with a well defined nuclear membrane and a typical spherical nucleolus. Special nuclear inclusions are mentioned which the author considered to have arisen from infoldings of the nuclear membrane. Processes could be traced from these cells for variable distances. In the cytoplasm the tigroid substance and neurofibrils were found in abundance. Vacuolation and granular degeneration were occasionally seen.

Glia cells and fibers were demonstrated in abundance by Mallory's method. Numerous unmyelinated nerve fibers forming a network about the ganglion cells were demonstrated with the reduced silver method. Other types of small round cells resembling lymphocytes were found in the regions about the blood vessels, apparently coming from the Virchow-Robin spaces. The author considered them as wandering cells.

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20. Achucarro, N.: Ganglioneurom des Zentralnervensystems, Folia Neurobiol. **7**:524, 1913.

Comment.—This case, studied by one who has been active in investigations of the cellular elements of the central nervous system, adds much to the knowledge of pathologic alterations in the ganglion cells as found in this type of tumor. The study of the nuclear inclusions is particularly complete. This tumor was the first one of its kind to be found in the cerebellum and like some of the cases studied later was associated with cystic degeneration.

CASE 6 (Schmincke [21]).—*Ganglioneuroma of the right temporal lobe.*

Clinical History and Physical Examination.—Unfortunately, very little of the history in the case was known, as the patient did not come under the personal

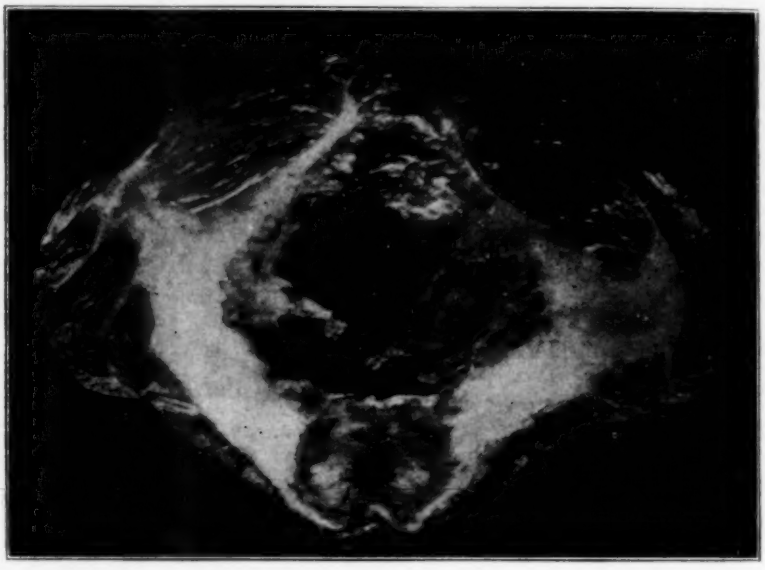

Fig. 2 (case 5).—Ganglioneuroma of the cerebellum. (After Achucarro.)

observation of Professor Schmincke. A professional acquaintance was called to see the patient, a boy, aged 17, just before his death. In addition to the fact that the boy was comatose, the only recorded observation was a bilateral papilledema.

Gross Pathology.—Because the brain had been removed and sectioned by a novice, the exact anatomic relationships were made out only with considerable difficulty. According to Schmincke, it was located in the outer portion of the anterior one third of the right temporal lobe. The growth was spherical, about the size of a walnut, and was sharply demarcated from the surrounding medullary substance by its grayish-white color and its granular, striated appearance. Its

21. Schmincke, Alexander: Ein Ganglioglioneurom des Grosshirns, Verhandl. d. deutsch. path. Gesellsch. **17**:537, 1914. In the discussion of Schmincke's study, Schmorl and Orsos mentioned having analogous cases, that of the latter being a tumor the size of the fist in the anterior part of the corpus callosum. As a detailed report of these cases is not furnished, they cannot be included in this series.

cut surface was mottled with reddish-yellow spots which proved to be small hemorrhages. Fine concentric striations were also found in the white substance surrounding the tumor.

Histopathology.—The tumor was composed of a network of fine fibrils in the meshwork of which were found cells of various sizes. This network, which varied in density in the preserved portions of the tumor, proved to be essentially neuroglial, as shown by specific stains. In this mass of fibers were found glia cells, the larger forms of which were called "monster glia cells."

The unipolar or bipolar ganglion cells with one or more vesicular nuclei were grouped together with other cells of smaller size in "developing nests." There were no typical tigroid granules, although some of the cells had a rather indistinct granular appearance. Of special interest in these cells is the occurrence of typical mitotic figures. The protoplasm of the ganglion cells in some cases showed vacuolization and contained dull-staining, poorly defined masses, evidently degenerative in nature. The smaller cells that occurred about the blood vessels were considered to be neuroblasts and gliablasts.

The nerve fibers as stained by Bielschowsky's method could be traced in some instances for some distance through the tissue. These fibers were often varicose and no side branches were to be seen. Together with the glia fibers, they composed the ground substance of the tumor. The tumor showed a rich vascularization and in many areas were found thrombosed vessels, usually associated with large or small areas of hemorrhage due to rupture of their thin capillary-like walls. Owing to the necrosis in the hemorrhagic areas, the tissue structure could not be made out.

Comment.—It is interesting to note in this case that the tumor had a location identical with that of the first case described by Schmincke (case 6); likewise, it occurred in a boy aged 17. The case was somewhat unusual in that it demonstrated the presence of mitotic figures; this is rare in this type of tumor and was not seen in any of the other cases in this series.

CASE 7 (Robertson [22]).—*Ganglioneuroma arising from the floor of the third ventricle.*

Clinical History.—A girl, aged 16, was admitted to the hospital complaining of headaches. For the previous nine months they had been particularly severe and of the fronto-occipital type, occurring chiefly on the left side of the head. The headaches were associated with dimness of vision and a marked tendency to dizziness and drowsiness. Vomiting had occurred but twice. There was definite weakness in the right arm and leg associated with paresthesias in these members. There was also weakness of the right side of the face. Treatment for a period of two weeks with potassium iodide was without effect, the condition becoming progressively worse. In spite of a decompressive operation over the left frontal lobe, the patient became blind. Examination of the eyes at this time showed an atrophy superimposed on a choked disk.

Physical Examination.—The patient was well proportioned and well developed and was almost totally blind. There was no disturbance of gait and no tremor,

22. Robertson, H. E.: Ein Fall von Ganglioglionеuroma am Boden des dritten Ventrikels mit Einbeziehung des Chiasma opticum, Virchows Arch. f. path. Anat. **220**:80, 1915.

but the right arm and leg were definitely weaker than those on the left. The pupils were widely dilated, the left being the larger. There was still some reaction to light in the left eye. The tongue deviated to the right side and was less sensitive on the right than on the left side. The mouth was drawn to the left side when speaking, and the facial folds were present only on the left side. Sensibility was diminished over the entire right side of the body, the abdominal reflexes being absent on that side. The right patellar reflex was increased and was associated with a homolateral patellar clonus and a Babinski sign.

On the left side of the forehead at the decompression site there was a soft, pulsating prominence the size of an apple. There was a semicircular scar of the skin on the front of the right thigh from which fascia had been taken for repair of the cranial defect. There were no changes in the condition of the patient during her stay in the hospital. She died rather suddenly.

Gross Pathology.—On removal of the skull cap, the brain and its coverings were found to protrude markedly from the decompression opening, the edges of which were worn smooth by pressure. At the base of the brain there was a recent hemorrhage which occupied the subarachnoid channels about the pons and medulla, extending downward into the vertebral canal. The floor of the third ventricle bulged out, presenting a firm tumor, the size of a plum, situated between the diverging limbs of the optic tracts (fig. 3). The tumor had resulted in an enlargement of the sella turcica and had compressed the pituitary gland into a thin plate of tissue. The growth extended posteriorly to the mammillary bodies but did not involve them. On sagittal section it was seen to extend upward into the third ventricle. The tumor was yellowish gray, and no necrosis, softening or hemorrhage was observed.

Histopathology.—Sections of the tumor revealed a fairly cellular structure with a fibrous ground substance. The tissue was fairly rich in blood vessels, thin-walled capillaries being especially conspicuous around the larger blood vessels and the capsule of the tumor. The neuroglia fibrils formed a meshwork surrounding the cellular masses. By the Bielschowsky silver impregnation method, unmyelinated nerve fibers were demonstrated in large numbers; in some areas they were arranged in parallel bundles and in others formed tangled masses. These fibers tended to have an uneven contour, to branch frequently and to pursue an irregular course.

The most conspicuous cellular element, the ganglion cell, varied greatly in size, form and staining qualities. The essential characteristics of ganglion cells were demonstrated—vesicular nuclei, Nissl's granules, dendrites and axons. Evidences of degeneration were noted: vacuolization, pigmentation, hyaline and calcareous degeneration.

Small lymphocyte-like cells, which constituted another element in the tumor, tended to collect about the blood vessels but were also found to be scattered diffusely throughout the tissue. Somewhat larger, round or oval cells were considered to be of glial nature.

Comment.—This tumor belongs to the group of gangliogliomas arising from the floor of the third ventricle between the mammillary bodies posteriorly and the optic chiasm and infundibulum anteriorly. Emphasis is laid on the degenerative forms, which are accorded a fairly complete study.

CASE 8 (Berblinger [23]).—*Ganglioneuroma of the septum pellucidum.*

Clinical History and Physical Examination.—A girl, aged 17, had suffered from severe headaches and was was almost totally blind, only faint light perception remaining. Before death, tonic-clonic convulsions made their appearance. Bilateral choked disks were found on examination.

Gross Pathology.—The tumor was a firm sessile growth, about the size of a nut, situated on the left side of the septum pellucidum; it extended over the

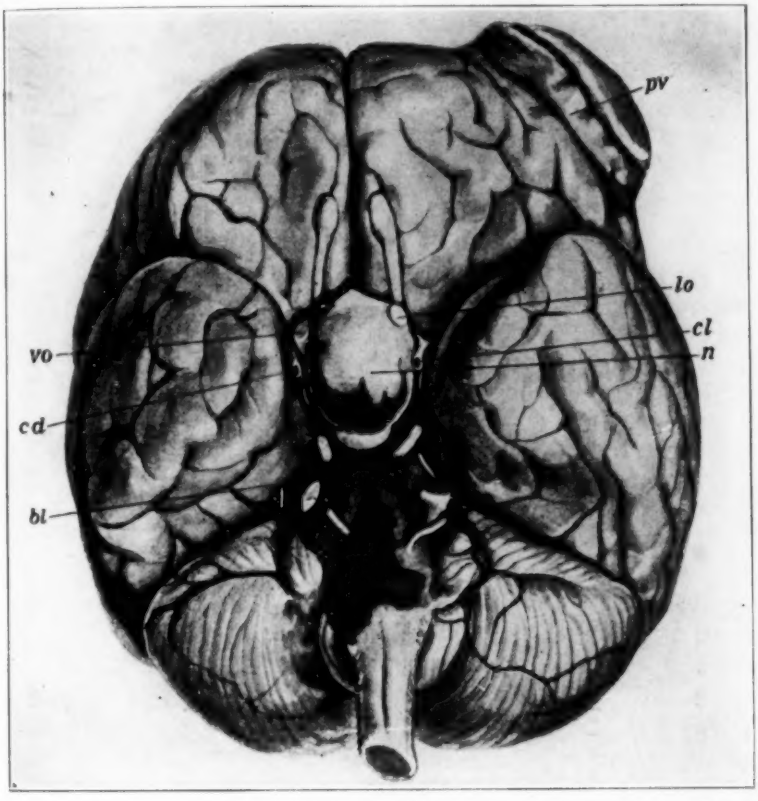

Fig. 3 (case 7).—Ganglioglioneuroma arising from the floor of the third ventricle. (After Robertson). *pv* indicates the cerebral hernia; *vo*, right optic nerve; *lo*, left optic nerve; *cd*, right internal carotid; *cl*, left internal carotid; *n*, tumor, and *bl*, basilar hemorrhage.

anterior pole of the left corpus striatum. On section, it was white, and the surface was marked by fairly large vessels and hemorrhagic areas.

Histopathology.—The tumor was composed essentially of large elements, the nuclei and processes of which were characteristic of ganglion cells. True Nissl's substance was not demonstrated, only a cytochromatic granulation being found in

23. Berblinger: Ganglioneurom des Gehirns, München. med. Wchnschr. **64:** 916 (July 10) 1917.

the protoplasm of some of the larger forms. This was attributed to the fact that the cells were not fully matured. Degeneration forms were observed which had a hyaline appearance and in these the nuclei were pyknotic or absent.

The stroma of the tumor was found to be composed of unmyelinated nerve fibers with some glial elements. In his discussion of the growth Berblinger considered that developing glia had a part in its proliferation.

Comment.—This rather brief description of a rare situation for this tumor is of interest. Unfortunately, a more detailed study of the microscopic structure of the tumor was not furnished. In view of its location one is caused to speculate as to the basis of its origin. Perhaps, as in the case of tumors arising from the tuber cinereum, this growth developed from primitive ganglion cells which were located in the septum pellucidum.

CASE 9 (Greenfield [24]).—*Ganglioneuroma of the base of the brain arising from the tuber cinereum.*

Clinical History.—Two and one-half years before admission to the hospital, the patient, a woman, aged 26, was seized with severe right-sided retro-orbital headaches. They came on shortly after the birth of a child and were associated with progressive loss of vision.

Physical Examination.—On admission the patient presented rather typical signs of acromegaly, with enlargement of the cranium, tongue, hands, feet and mandible. There was brown pigmentation of the skin of the axillae and of the abdomen. The patient died a week after a second admission to the hospital.

Gross Pathology.—The whole base of the brain was covered with an irregular tumor mass, the nodules being more or less distinct from one another, but joined by their capsules. The whole mass reached from the olfactory bulbs to the anterior inferior surface of the pons.

"Over the region of the olfactory bulbs the tumor has to some extent been removed (by operation). Posterior to this the tumor mass is diffusely stained with haemorrhages, and extends anteroposteriorly for 9 cm., laterally for 5 cm., vertically the greatest measurement is 4.5 cm. (fig. 4).

"Of individual tumor nodules the largest measures 3 cm. in diameter, the smallest 7 mm. They do not infiltrate the brain at any part, being loosely attached to the meninges.

"No trace of the pituitary body can be found. The tumors are pressed more into the right frontal and temporal lobes than the left; they push the right temporal lobe altogether aside from the crus cerebri on that side."

Histopathology.—The tumor was composed of large and small cells lying in a matrix of loose tissue. The large multipolar cells contained one or more vesicular nuclei, in each of which was found a round darkly staining nucleolus. Although typical Nissl's substance was not observed, they were evidently ganglion cells. The small round cells with scanty cytoplasm were considered to be neurocytes.

When studied by specific methods, the stroma was found to be composed of connective tissue and nerve fibers. By Bielschowsky's method the unmyelinated nerve fibers were found to arise from the small as well as from the large cells.

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24. Greenfield, J. Godwin: The Pathological Examination of Forty Intracranial Neoplasms, Brain **42**:29, 1919.

Some myelinated nerve fibers were also seen which were considered to be from the cranial nerves infiltrated by the tumor. No glia fibers were found, although elements were observed which resembled those occurring in the neurofibromas and were thought to be derived from the sheath cells. The blood vessels were well formed and were supported by a condensation of tumor tissue. The large channels had a well defined fibrous connective tissue wall.

Comment.—This case, the second found with an origin in the floor of the third ventricle, is extraordinary in the association of multiple

Fig. 4 (case 9).—Ganglioneuroma of the base of the brain. (After Greenfield.)

small polypoid nodules at the base of the frontal lobes with the larger tumor. It is possible that they were extensions from the original growth through the subarachnoid space. It is also the only one in the series in which removal of the tumor was attempted.

The occurrence of acromegaly was also a confusing factor, the patient presenting a typical syndrome of hyperpituitarism. No trace of the pituitary body was found at autopsy, so the presence of an associated pituitary adenoma was not demonstrated.

CASE 10 (Olivecrona [25]). — *Ganglioglioneuroma myelinicum of the right parietal lobe.*

Clinical History.—A laborer, aged 39, was taken suddenly sick about a week before death with severe headaches which radiated down the back of the neck. Two days before death, he became drowsy and sank into a comatose state from which he did not rally.

Gross Pathology.—When the skull was opened, the dura mater was found to be under marked tension and the convolutions of the brain, especially of the right hemisphere, were definitely flattened. Cross-sections though the hemispheres showed that the ventricles were much dilated, their ependymal lining being marked by small granulations. In the middle of the right parietal lobe was a firm, reddish-gray mass, about 7 cm. long and 6 cm. in diameter, which was not sharply demarcated from the overlying cortex.

Histopathology.—The tumor tissue was composed of a fibrous ground substance in which various types of cells and numerous nerve fibers were embedded. With van Gieson's stain many of the fibers were shown to be connective tissue. Specific methods did not give satisfactory results, but, from the morphology of the associated cells, glia fibers were considered to be present in the stroma. Bielschowsky's method showed that some of the nerve fibers were unmyelinated, but most of them had a myelin sheath. Varicose swellings in the latter indicated that degenerative changes were taking place.

The most conspicuous cellular elements were large round or oval forms, of variable size, with one or more vesicular nuclei. The protoplasm appeared to be completely homogeneous, no chromatophilic granules or fibrils being demonstrated by specific methods. Degeneration forms were numerous, and were evidenced by granular bodies within the cell or by karyolytic or pyknotic changes in the nuclei. Other multipolar forms, morphologically resembling ganglion cells, were considered to be malformed neurocytes of Golgi type II.

In the more fibrous areas of the tumor, many small cells with oval or elliptic nuclei were observed, the protoplasm of which stained reddish violet by Mallory's aniline blue-orange method. They had a tendency to be arranged in long rows or in protoplasmic bands and were thought by the author to be sheath cells of Schwann. Scattered through the tissue were still other small lymphocyte-like cells which were believed to be glia cells, even though the methods used did not result in typical staining reactions.

Comment.—The presence of myelinated nerve fibers in this case is of special interest. In only two other cases in the series was a true neoplastic proliferation of myelinated fibers (Dumas, Lhermitte and Duclos) found. As suggested by Olivecrona, this may be evidence of the mature nature of the tumor. He gave as additional proof that no embryonic forms of ganglion cells were observed.

Another interesting conjecture is that the oval or elliptic cells arranged in rows were sheath cells of Schwann. This idea is echoed by Bielschowsky and Henneberg in the discussion of their cases when they compared the structure of the tumors studied by them to periph-

25. Olivecrona, Herbert: Zwei Ganglioneurome des Grosshirns, Virchows Arch. f. path. Anat. **226**:1, 1919.

eral neurinomas. Because of the impairment of the staining qualities of the tissue, the necropsy having been performed forty-eight hours post mortem, positive proof cannot be derived from the evidence presented as to the true nature of these cells. It is difficult to conceive how sheath cells, not normally found in the central nervous system, could have a part in the proliferation of a subcortical tumor.

One cannot help but wonder whether the ependymal granulations referred to might not be miniature tumors, such as were described by Bielschowsky in his case of multiple gangliogliomas of the brain.

CASE 11 (Olivecrona [25]).—*Ganglioglioneuroma of the right frontal lobe extending into the left frontal lobe.*

Clinical History.—"From the clinical standpoint, we can only say that the tumor was found in a woman who had suffered from a spastic paralysis of the left arm."

Gross Pathology.—"The autopsy report states that the tumor was located in the inferior part of the right frontal lobe, extending also into the left frontal lobe. A small piece of this tumor had been sent in for microscopic examination. Regarding the block of this tumor which was in formalin, we can only say that macroscopically it was of reddish-gray to whitish-gray color and apparently of firm consistency."

Histopathology.—Sections showed the structure to be much like that in case 10 (Olivecrona), cells embedded in a fibrous stroma composed of connective tissue, unmyelinated nerve fibers and probably glia fibers. The last named element could not be verified because of the failure of specific methods to demonstrate their presence. The nerve fibers branched frequently and formed fine collaterals.

Large round or polyhedric cells with one or more vesicular nuclei were the most conspicuous cell forms. The chromatin material of the nucleus was condensed into one or more nucleoli. Dumbbell forms and invaginations of the nuclear membrane gave evidence of cell division. The protoplasm was completely homogeneous, tigroid granules not being found by appropriate stains. In some cells a fibrillary differentiation was observed which could be traced into the larger processes. Other smaller cells, the nuclei of which resembled those of ganglion cells, were considered neuroblasts. Mitoses were not observed.

Scattered between the ganglion cells, numerous other small lymphocyte-like cells were found. Their nuclei, comparatively rich in chromatin, occupied most of the cell, protoplasm at times being limited to a fine border. From their morphologic characteristics they were considered to be glia.

The tumor was richly supplied with small capillary blood vessels, many of which were thrombosed. This probably accounted for the numerous areas of necrosis found throughout the sections. Phagocytic cells containing fat were scattered throughout the tissue.

Comment.—From the large number of ganglion cells and the small amount of intercellular substance the author concluded that this tumor was less mature than the first one he studied (case 10). As before, the presence of glia was presumed only from the morphologic characteristics. The location of the tumor is of interest, this being the only

verified one in the frontal lobe. Orsos, in discussing case 6, mentioned a tumor having the general characteristics of a ganglioglioma which was found in the anterior part of the corpus callosum. It may have been a similar case.

CASE 12 (Lhermitte and Duclos [26]).—*Diffuse ganglioneuroma of the cerebellar cortex.*

Clinical History.—A man, aged 36, entered the hospital complaining of occipital headache, dizziness, diminished acuity of hearing in the left ear and difficulty in walking. The past history was essentially unimportant except for a cranial injury sustained during childhood. The first symptom noted by the patient was failing auditory acuity in the left ear; this was followed in a short time by occipital headaches. In the course of a year, vertigo and ataxia became so marked as to compel him to leave work. Mental symptoms, such as loss of memory, confusion and disorientation, became a prominent feature of the illness and he was consequently transferred to a hospital for the mentally defective.

Physical Examination.—At the time of admission, the patient was markedly ataxic in all extremities, which made it impossible for him to walk or feed himself. Adiadokokinesis was present. Nystagmus was observed when the eyes were turned in any direction. The pupils were unequal, the left being the larger. All sensory modalities were intact. The deep reflexes were exaggerated throughout, and ankle clonus was present on both sides.

As the patient became progressively worse, symptoms suggesting an increase in intracranial tension became prominent: slowing of the pulse, vomiting and excruciating headache. Dysphagia and dysarthria were also observed. He died in coma two weeks after admission to the hospital and about a year after the onset of symptoms.

Gross Pathology.—The brain was edematous, and the convolutions were definitely flattened. A bloody effusion was found in the sylvian fissure on both sides. The cerebellum was definitely asymmetrical, the gyri of the left hemisphere being hypertrophied, firmer in consistency and paler than the right. In this change, however, the normal shape and relationships were preserved (fig. 5). The enlargement was confined to the cortex, the underlying white lamina and dentate nucleus being definitely diminished in volume.

Histopathology.—Sections of the hypertrophied area demonstrated two well defined zones: a superficial one containing a feltwork of nerve fibers and a deeper layer of newly formed cells from which the fibers in the superficial layer had their origin. The normal constituents were entirely absent in the tumor area. The fibers stained deeply with reduced silver after the method of Nageotte. The cells were morphologically characteristic of ganglion cells, having for the most part a pyramidal shape. The nucleus was large and vesicular and contained a single round nucleolus. Nissl's stain demonstrated the presence of chromophile granulations found usually in the peripheral portions of the cytoplasm. No evidences of either direct or indirect cell division were discovered.

The vessels in the tumor presented no marked changes and perivascular round cell infiltration, so often observed by other writers, was entirely absent. Small areas of edema were found here and there in the newly formed tissue.

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26. Lhermitte, J., and Duclos: Sur un ganglioneurome diffus du cortex du cervelet, Bull. de l'Assoc. franç. p. l'étude du cancer **9**:99 (April 19) 1920.

Comment.—This case differs from the others in the series in that the neoplasm does not appear as a definite tumor but rather as a hypertrophy of the existing gyri. The author stated that "it is a question here of a new growth having for its point of departure one of the congenital malformations which are known to be present frequently and with variety in the cortex of the cerebellum." It is not unlikely that the tumor arose from some heterotopic condition which, with a proper stimulus, assumed a neoplastic nature. The presence of an

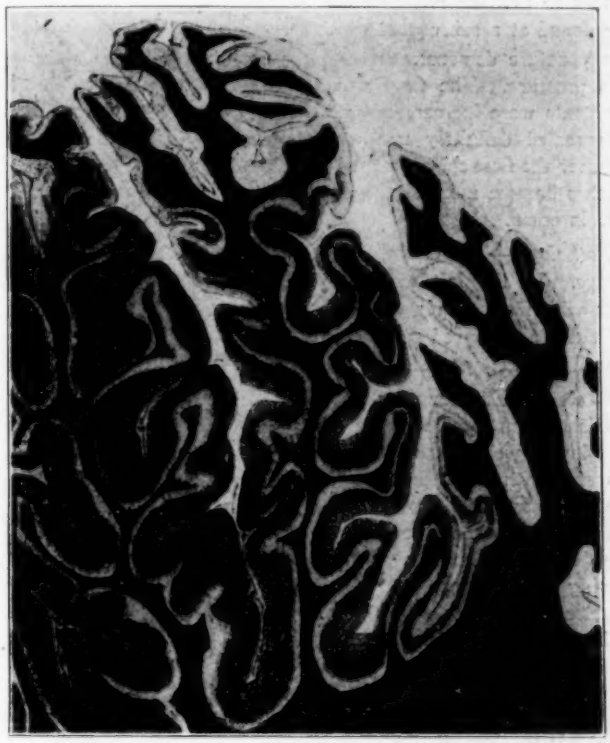

Fig. 5 (case 12).—Diffuse ganglioneuroma of the cerebellar cortex. (After Lhermitte and Duclos.)

increasing pressure syndrome which brought about the death of the patient is evidence that the lesion was a true tumor at the time when it was studied at necropsy and was not a heterotopic manifestation.

CASE 13 (Bielschowsky [27]).—*Multiple ganglioneuromas of the brain.*

Clinical History.—A laborer, aged 26, had had severe headaches since the age of 11. The present illness began with a transient pain over the right eye which

27. Bielschowsky, Max: Das multiple Ganglioneurom des Gehirns und seine Entstehung, Jahrb. f. Psychol. u. Neurol. **32**:1, 1925.

recurred each morning with greater intensity and longer duration. Three weeks later, the patient noted blurring of vision and double vision which became persistent and gave him a feeling of insecurity while on his feet. He was admitted to the hospital in this condition.

Physical Examination.—Inspection revealed a moderately well nourished and well developed man, who presented no external evidence of visceral disease. The pupils were regular and reacted to light and in accommodation. Rotary nystagmus and definite weakness of the right internal rectus were noted. The superficial reflexes showed no abnormalities. Ataxia was marked in the lower extremities on attempting to flex the knees or on walking. Papilledema with retinal hemorrhages was found at a subsequent examination.

Lumbar puncture demonstrated that the cerebrospinal fluid was under marked increase in pressure. The fluid was clear and colorless, and the albumin and globulin contents were increased. The Wassermann reaction was negative. Later punctures revealed definitely xanthochromic fluid. The patient improved for a short time after the first spinal puncture, but his condition soon became much worse. The headaches became more intense, mental symptoms became prominent, and the patient died in coma.

Gross Pathology.—The convolutions of the brain were flattened as a result of hydrocephalus. In the left cerebellopontile angle was a reddish-gray, nodular tumor mass which was fairly easily separated from the brain substance. Cross-sections of the brain showed many small tumors, up to the size of a lentil, arising from the walls of the ventricles and the cerebral aqueduct.

Histopathology.—Examination of the small tumors protruding from the ventricular walls demonstrated that they were absolutely similar in structure. Two well defined layers were present: a superficial one adjacent to the ventricle which was not covered with ependyma, and a deeper layer composed of cells embedded in a fibrillary network. The outer layer contained glia cells and fibers, resembling the subpial condensation of supporting elements found in the normal brain. The cells in the deeper zone were characteristic of ganglion cells of various sizes and shapes, having a clear round nucleus within which was found a round deeply staining nucleolus. Nissl's granules and neurofibrils were demonstrated in the cytoplasm by appropriate stains. Atypical developmental forms were observed in some parts of this layer. The fibrillary network was composed of many unmyelinated nerve fibers and a few glia fibers.

The tumor in the left cerebellopontile angle apparently had its origin in the "area parolivaris lateralis," and extended laterally, embedding the roots of the glossopharyngeal and vagus nerves and involving the gyri of the adjacent portion of the cerebellum (fig. 6). The part of the growth in the vicinity of the medulla was extremely cellular while the more lateral portion was composed of a network of glia fibers. This tumor nodule was filled with cysts, and in the areas surrounding the blood vessels many calcareous concretions were found.

A third tumor, which proved to be of great interest, was found invading the pons, extending downward from the rhomboid fossa. The upper portion presented a tumor nodule which extended into the fourth ventricle. In this nodule were neuroblasts and ganglion cells. In the more ventral areas these cells had an epithelial arrangement and in some cases formed rosets. In the midline of the tumor was a streak of spindle cells with rod-shaped nuclei, the nature of which the author did not make clear.

Comment.—This case has many unique features which have not been observed in any other case reported in this series. The nearest approach to multiple ganglioneuromas of the central nervous system was in the case of Greenfield in which there was a large tumor arising from the tuber cinereum with many small nodules in the arachnoid on the ventral surface of the frontal lobes. The ventricular tumors with their peculiar construction were considered to be areas which, in fetal life, developed toward the ventricular cavity instead of the periphery of the neural tube. "In this way a second brain cortex has developed

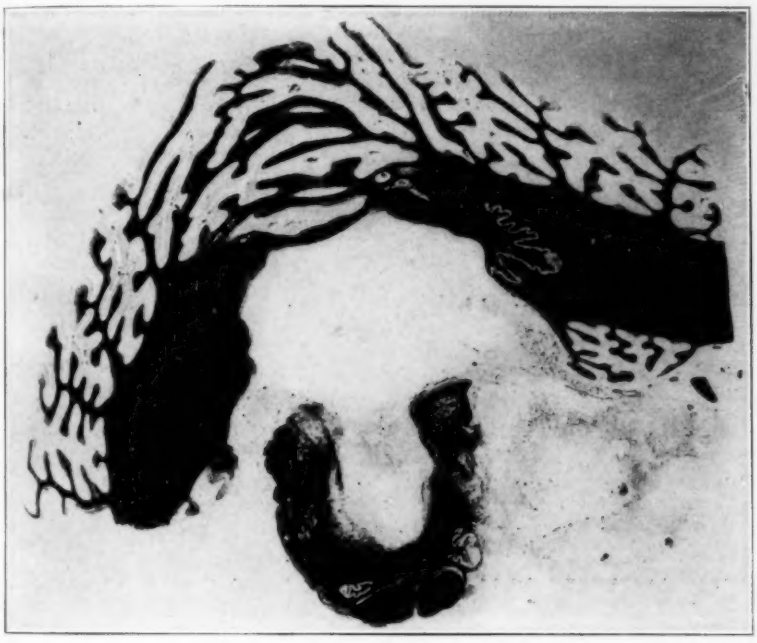

Fig. 6 (case 13).—Multiple ganglioneuromas of the brain. Section through the cerebellum and medulla shows tumor nodules in the pons and in the cerebellopontile angle. (After Bielschowsky.)

on the inner ventricular wall of the vesicle of the hemisphere." The comparison of the structure of the tumor to the embryonic brain and the absence of an ependymal layer over the new growth seemed to confirm this opinion. The presence of the cerebellopontile angle tumor was explained on the basis of the theory of Marburg [28] who attributed the origin of tumors in this region to cells which maintain a primitive

28. Marburg, O.: Studien über den Kleinhirnbrückenwinkel und den hintern Kleinhirnabschnitt, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **24**:1, 1922; quoted by Bielschowsky (footnote 27).

state throughout life. Bielschowsky believed that Cohnheim's theory of cell inclusions is to be definitely considered as a basis of etiology of tumors of the central nervous system.

CASE 14 (Perkins [29]).—*Ganglioglioma of the floor of the third ventricle.*

Clinical History.—A boy, aged 16, was admitted to the Long Island College Hospital complaining of headache, vomiting and drowsiness. He had been perfectly well up to the onset of the illness and had progressed rapidly in school. The first symptoms were headache and blurred vision, which began two and a half weeks before entrance to the hospital, and were soon followed by projectile vomiting and drowsiness. He was admitted in a semistuporous condition and died two days later.

Physical Examination.—The patient was fairly well nourished and was in a semiconscious state but could be roused for a short time. With the exception of a cardiac murmur, systolic at the apex and diastolic at the base, there were no general physical abnormalities. There was some weakness of the right fourth, sixth and seventh nerves. The right patellar reflex was hyperactive and the Babinski sign was positive on the right side. No other neurologic observations were recorded.

Lumbar puncture revealed spinal fluid under slightly increased pressure. The cell count was 200, 70 per cent of which were lymphocytes and 30 per cent polymorphonuclear leukocytes. Blood studies revealed a leukocytosis of 18,000.

Gross Pathology.—On the ventral surface of the brain the mammillary bodies were crowded posteriorly into the interpeduncular space. When the third ventricle was opened, a tumor, 3 by 4 by 2.5 cm., was found protruding from its floor (fig. 7). It was purplish and firm. Owing to its position, it had occluded the interventricular foramina and caused dilatation of the lateral ventricles. It extended posteriorly into the tegmentum of the midbrain, involving the red nucleus on both sides and compressing the cerebral peduncles. Certain portions of the tumor contained calcified particles.

Histopathology.—Sections of the neoplasm showed islands of large cells separated by a fibrous-like stroma. The cells varied greatly in size, were usually multipolar and contained several vesicular nuclei, indicating a tendency to direct cell division. More isolated cells were bipolar and contained a single nucleus. Chromophilic granules were found in the cytoplasm, especially beneath the cell membrane. Other darkly staining cells, which were difficult to identify, were observed scattered throughout the matrix. The author considered them to be neuroglia cells.

The stroma of the tumor formed a large part of the mass and was composed of a network of fibers, which were considered to be unmyelinated nerve fibers and probably embryonic neuroglial fibers or young connective tissue fibrils. There was no evidence of cystic degeneration. Many well formed blood vessels were found throughout the tumor.

Comment.—This is still another case in which the tumor had its origin in the floor of the third ventricle. The short course of the symptoms, less than three weeks in all, is of interest. The abrupt onset and short course were probably due to a sudden block of the

29. Perkins, Orman C.: Ganglioglioma, Arch. Path. & Lab. Med. **2**:11 (July) 1926.

interventricular foramina with resultant acute hydrocephalus. While selective stains were not utilized in the microscopic study of the tumor, it is undoubtedly a ganglioglioma. Specific methods would probably have revealed glial elements in addition to the others described.

CASE 15 (Marinesco [30]).—*Neurocytoma (ganglioneuroma) of the infundibular region.*

Clinical History.—"As described by Bacaloglu and Parhon,[31] the case is that of a woman, aged 40, who had been diabetic for many years, and died after having had epileptiform convulsions; at autopsy we found a tumor the size of a pigeon's egg in the infundibular region and adherent to the left hippocampal convolution"

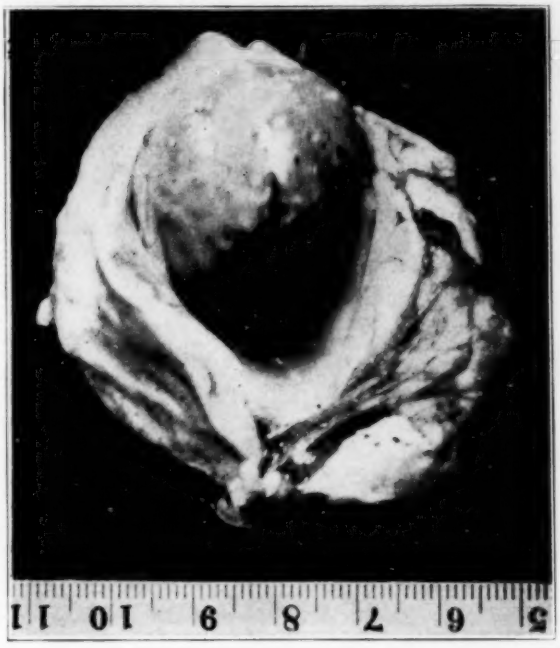

Fig. 7 (case 14).—Ganglioglioma of the floor of the third ventricle. (After Perkins.)

Histopathology.—Microscopic study of the tumor revealed two distinct regions; a superficial portion consisting chiefly of cells of nerve and glial type and a deeper portion composed of tangled bundles of fibers. In his more detailed description, Marinesco directed attention especially to the nerve cells which were morphologically characteristic. They were grouped according to their size into large, medium and small cells. The nuclei, which were large and clear staining,

30. Marinesco, G.: Sur un cyto-neurome de la région infundibulaire (ganglioneuroma), Ann. de méd. **20**:577 (Dec.) 1926.

31. Bacaloglu, C., and Parhon, C.: Polynucléose neurocytaire et division amitotique des cellules nerveuses dans un cas de tumeur primitive de la région infundibulaire, Compt. rend. Soc. de biol. **94**:714 (Feb. 3) 1926.

contained one or two round basophilic nucleoli. In some cells as many as seven or eight nuclei were observed and many showed evidences of incomplete division. Neurofibrils were demonstrated in the cytoplasm of the cell by the methods of Bielschowsky and Cajal. Nissl's substance of atypical character was present, sometimes arranged in a ring about the periphery of the cell as is found in cells undergoing chromatolysis. A structure resembling Golgi's reticular apparatus, having a perinuclear or a polar location, was found in some of the cells. Degenerative changes of an amyloid or hyaline nature, as well as vacuolization of the cytoplasm, were observed.

In between the cells, as well as in the deeper portions of the tumor, a tangled network of fibers was observed. These fibers proved to be unmyelinated nerve fibers arising from the dendrites and the axons of the nerve cells. No myelinated fibers were observed. In the cellular regions of the tumor the tissue about the vessels was infiltrated with round cells and a few plasma cells. This phenomenon was attributed to the elaboration of a chemotactic irritative substance by the tumor which resulted in the perivascular infiltration of the wandering cells.

Comment.—This tumor is undoubtedly a ganglioglioma and had its origin in the floor of the third ventricle. The briefly described symptoms are much like those in other cases of this type. The author has given a complete study of the nerve cells of the tumor but has little to say of the cells of neuroglial type or of the occurrence of immature forms.

CASE 16 (Horrax and Bailey.[32]).—*Ganglioneuroma replacing pineal body.*

Clinical History.—A man, aged 40, had suffered from frontal headaches for the previous fifteen months. Vision had been failing for a year, being especially conspicuous for the four months previous to admission to the hospital. For this same period he had been drowsy; marked staggering in the gait had been experienced and at the time of entrance he could not walk. During the last three months, he had had two attacks characterized by numbness of the right side of the face, and the right arm and leg. Dysphagia and dysarthria were late symptoms.

Examination.—The patient was well developed and rather somnolent; he had bilateral choking of the disks of from 4 to 5 diopters, and vision was almost gone. The pupils were unequal, the left being larger than the right. Reaction to light was absent in both eyes. Conjugate movement of the eyes was impossible upward or downward. The deep reflexes were exaggerated throughout, associated with bilateral ankle clonus and Babinski's sign. Dysphagia and dysarthria were evident.

The patient died three days after a palliative suboccipital decompression.

Gross Pathology.—The brain, hardened in situ by the injection of formaldehyde through the carotids, on sagittal section showed a small, flattened, circumscribed tumor of the pineal body which measured 7 by 18 mm. (fig. 8).

Histopathology.—"Microscopically the tumor was composed of scattered nerve cells in all stages of development, and between them were other cells of indifferent character. A few small blood vessels were scattered about, and numerous calcospherites were present. The nerve cells were of all sizes and shapes, many of them multinucleated. They contained often, in the periphery of their cytoplasm, dustlike particles which stained with methylene blue but rarely well formed Nissl

32. Horrax, Gilbert; and Bailey, Percival: Pineal Pathology: Further Studies, Arch. Neurol. & Psychiat. **19**:400 (March) 1928.

bodies. The nuclei were large, spherical and vesicular, with one or two large nucleoli and little chromatin. Many of them had long branching processes in which neurofibrils were impregnated. In the cell body, the neurofibrils were not clearly demonstrated. Myelin sheaths were not present.

"The other cells of the tumor were probably to be considered as neuroglial. Most of them were bipolar, with oval nuclei having a delicate reticular network. Some were star-shaped. Their processes were sometimes stained with ethyl violet and were better seen by Hortega's fourth variant or phosphotungstic acid-hematoxylin. Other interstitial cells had elongated heavily stained nuclei resembling those of the microglia. The method of fixation precluded their positive identification as such.

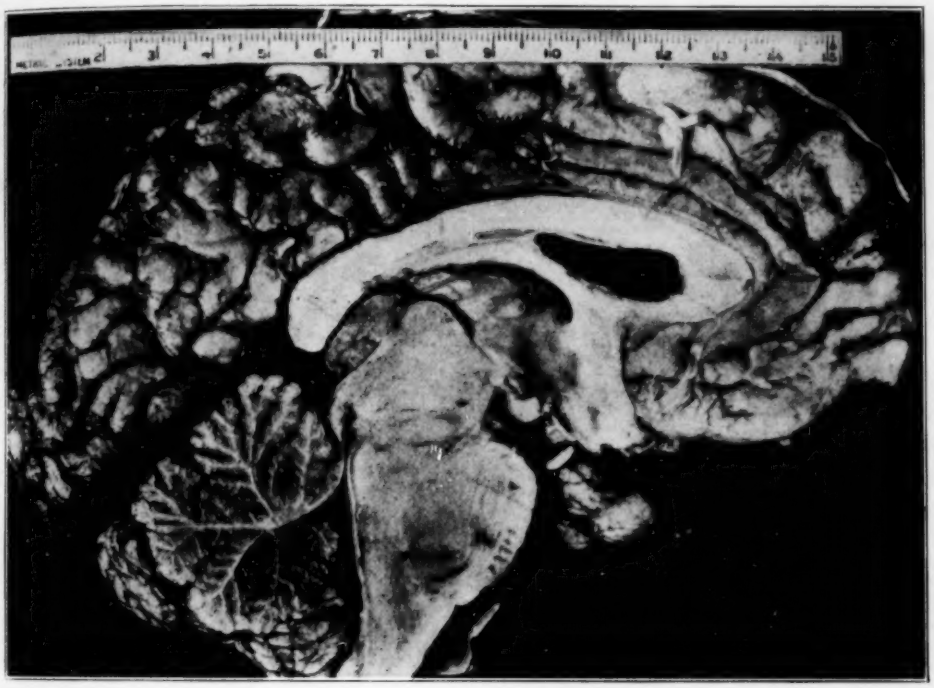

Fig. 8 (case 16).—Ganglioneuroma replacing pineal body. (After Horrax and Bailey).

"Nowhere were there any cells of the pineal parenchyma and nothing resembling the normal structure of the pineal body. The tumor was a typical ganglioneuroma."

Comment.—This case is indeed a rarity, no other one of this type having been discovered in this region. The authors raised the question as to its possible origin, as nerve cells are not to be found in the normal adult pineal body. They stated that "the pineal anlage has a potentiality for developing nerve cells, whether or not this happens in normal development." It is suggestive that potential ganglion cells, which

pursue an aberrant course of development, are the essential cause of this type of tumor.

CASE 17 (Bielschowsky and Henneberg [33]).—*Ganglioneuroma of the left temporal lobe extending into the infundibular region.*

Clinical History.—A girl, aged 16, had suffered from headaches since the age of 5. Nine months before death, the pain became intense and was associated with blurring of vision. She became drowsy, and weakness of the right arm and leg was noted. Six months before death she suddenly became blind, and choked disk was observed on ophthalmologic examination.

Physical Examination.—Six months before death, it was found that the pupils were unequal in size, the left being larger than the right. She was totally blind in the left eye, vision in the right being markedly diminished. The tongue deviated to the right and was less sensitive on the weakened side. Right hemihypesthesia, absent right abdominal reflex, right patellar clonus and a right Babinski sign were also present.

Gross Pathology.—A tumor mass, slightly larger than a walnut, was found in the angle between the infundibular region and the temporal lobe on the left side. It had stretched the optic tracts and chiasm until they were very thin. It extended posteriorly into the interpeduncular fossa, while medially it protruded into a smooth-walled cyst the size of an apple located within the left temporal lobe. It was separated from the left lateral ventricle by a very thin wall composed essentially of compressed white substance.

The brain was cut in a series of frontal sections and showed the tumor and its relations to surrounding structures. It was found to have its origin in the roof of the inferior horn of the left lateral ventricle and extended medially into the interpeduncular fossa, secondarily giving it the appearance of a tumor arising from the tuber cinereum (fig. 9).

Histopathology.—The tumor was found to be made up of two areas of different structure: a bandlike zone having an alveolar arrangement lying adjacent to the ventricle, while the remainder of the tumor had the appearance of fiber fascicles. The first zone was composed of fairly typical ganglion cells, some of which were undergoing regressive changes, lying within a stroma composed of unmyelinated nerve fibers and connective tissue. These cells contained two or more vesicular nuclei and in the cytoplasm chromatophil masses and neurofibrils were found. In addition to the nerve fibers and connective tissue, specific stains demonstrated the presence of glia cells and fibers.

The greater portion of the tumor, however, was composed of fascicles of glia fibers between which a loose reticular structure was found. Throughout the tissue were scattered spindle-shaped glia cells and lymphocyte-like cells. Small narrow or oval cystic cavities were found in this portion of the tumor which in the main resembled a neurinoma.

Comment.—At first appearance the tumor seemed to have its origin from the region of the infundibulum, but further study demonstrated it to be located primarily in the roof of the inferior horn of the lateral

33. Bielschowsky, Max, and Henneberg, Richard: Ueber Bau und Histogenese der zentralen Gangliogliomeurome, Monatschr. f. Psychiat. u. Neurol. **68**:21 (March) 1928.

ventricle. From the comparatively common occurrence of this tumor in the temporal lobe it would seem that there must be a close relationship between the histogenesis of this part of the brain and the misplacement or maldevelopment of ganglion cells. The authors called attention to the presence of a large amount of connective tissue in the tumor and believed it to be due to a neoplastic proliferation of the normally large amounts of it in the roof of the ventricle.

The occurrence of the cyst cavity in this case calls to mind that of Worcester and that in my case.

CASE 18 (Bielschowsky and Henneberg [33]).—*Ganglioglioneuroma of the right temporal lobe.*

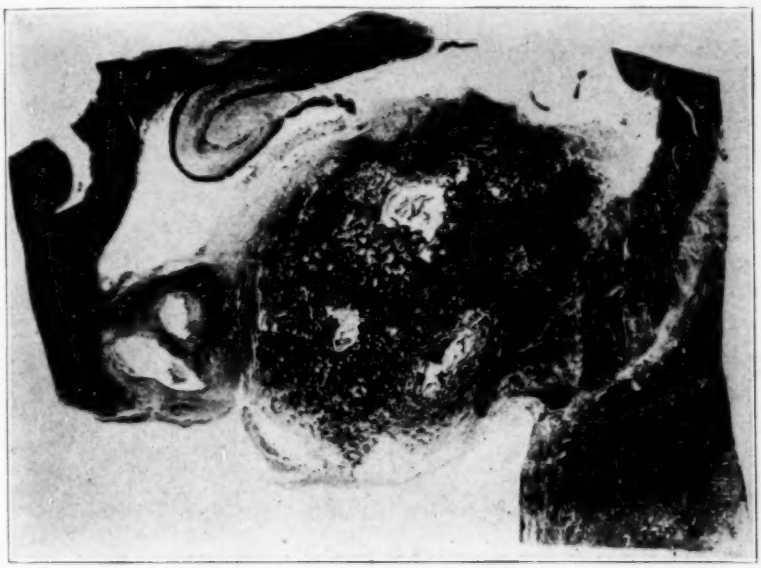

Fig. 9 (case 17).—Ganglioglioneuroma of the left temporal lobe. (After Bielschowsky and Henneberg.)

Clinical History.—A girl, aged 11, was admitted to the neurologic service of the Charité complaining of epileptiform seizures. They had begun when she was 4 years of age in the form of momentary lapses of consciousness. At the age of 6 they occurred as frequently as six attacks a day. They were ushered in by a feeling of fear, followed by vertigo, clenching of the fists, falling to the floor, biting of the tongue and cyanosis. Following the attack she would sleep for hours. Periods of confusion, characterized by aimless wanderings, were observed.

Several of the attacks occurred while the patient was on the ward and these were characterized by an onset of dizziness or by short spells of unconsciousness. After discharge from the hospital she became worse, the seizures being of a convulsive nature. The attacks ceased when the menses began but at the same time marked diminution of auditory and visual acuity was reported. Because of the rapidly failing vision she was brought to the hospital for a decompression operation.

Physical Examination.—The patient was well nourished and of moderate size. She had advanced secondary optic atrophy, being completely blind in the left eye and almost so in the right. Almost complete loss of hearing was present, only slight retention of bone conduction being found on the right side. Because of high fever and pain in the left ear, which were associated with a clouding and redness of the drum, a paracentesis was done and pus was evacuated. Lumbar puncture at this time showed a pressure of 24.5 cm. Later, a mastoidectomy was done under mixed narcosis. A second spinal puncture after this operation showed an increase in pressure up to 50 cm. The patient died on the second day after the operation.

Gross Pathology.—The cranial vault was thickened and its inner table roughened. The gyri of the cerebrum were flattened from increased tension. In the temporal lobe of the right side a fluctuant area was noted, apparently a cystic cavity within the hemisphere. The brain, after being hardened in formaldehyde, was cut in frontal

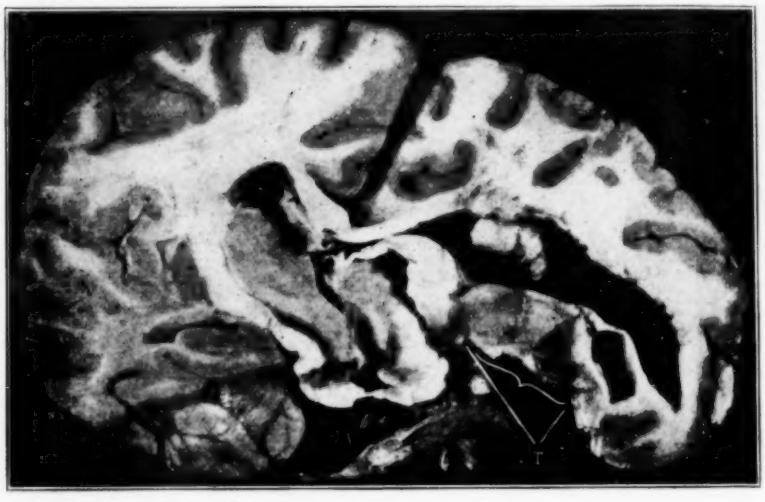

Fig. 10 (case 18).—Ganglioglioneuroma of the right temporal lobe. (After Bielschowsky and Henneberg.)

sections. A smooth-walled cystic cavity, about the size of a fist, formed of the dilated posterior and inferior horns of the right lateral ventricle, was found to correspond to the fluctuant area noted on external examination. A tumor, about 2.5 cm. in its longest diameter, was found arising from the lateral third of the hippocampal gyrus and inserted between it and the fusiform gyrus (fig. 10). An associated cyst, the size of a cherry, was found in the fusiform gyrus adjacent to the tumor.

On the ventral surface of the right cerebellar hemisphere was an area of thickening with a milky appearance, which, on microscopic examination, had a structure similar to the large tumor and was considered to be a metastasis from it.

Histopathology.—The large tumor nodule was composed of two superimposed zones. The ventral one, adjacent to the pia, contained a dense connective tissue stroma in which ganglion cells, glia cells and nerve fibers were present. A dorsal zone contained, for the most part, fascicularly arranged glial elements.

The multiform ganglion cells, located in alveolar-like spaces in the stroma, contained one or more vesicular nuclei in which there was a dark spherical central nucleolus. Neurofibrils and Nissl's granules were demonstrated with specific stains. Dendrites and axons were observed, the latter being traceable for some distance in the network. Regressive changes were found in these cells, such as pigmentary and fatty degeneration of the cell body.

Nerve fibers, forming a conspicuous element in the stroma, were demonstrated by the silver methods. As in other cases described by Bielschowsky and his co-workers, they were presumed to be products of the ganglion cell. The glia elements were most conspicuous in the ventral zone, and were associated there with connective tissue fibers. Well defined glia fibers were shown by Holzer's stain. The nuclei of the astrocytes were arranged in rows and resembled the architecture of neurinomas. In this zone the connective tissue elements had their origin from the pia mater covering the temporal lobe. They were believed to have a part in the neoplastic expansion of the tumor.

The margins of the tumor were not sharply outlined, merging rather imperceptibly into the surrounding tissue. In the adjacent zones were calcareous mulberry-shaped concretions which infiltrated the capillary walls. Their presence was supposed to be conditioned by the diminished oxygen-carbon dioxide exchange incident to the presence of the tumor.

The nodule on the inferior cerebellar surface contained characteristic ganglion cells embedded in a stroma of nerve fibers, glia fibers and connective tissue. No direct connection with the parent growth could be traced and it was believed to be a metastatic tumor reaching this situation through the subarachnoid space.

Comment.—The temporal lobe is another common situation for this tumor, being second only to the tuber cinereum. In this case the tumor was associated with a smooth-walled cyst, the origin of which was not suggested by the authors. As in their first case the abundance of connective tissue was regarded as a neoplastic proliferation.

Of interest is the similarity of the microscopic picture in some parts of the tumor to that of peripheral neurinomas. The idea of a possible association was stressed first by Olivecrona, who believed that the oval cells in rows were sheath cells of Schwann. Bielschowsky and Henneberg considered these cells to be astrocytes.

REPORT OF PERSONAL CASES

CASE 19.—*Ganglioglioma arising from the tuber cinereum.*

Clinical History.—A school girl, aged 15, was admitted to the Los Angeles General Hospital in an unconscious state, with right-sided jacksonian convulsions. The history revealed that at birth she was cross-eyed and took nourishment poorly for the first three months. At the age of 4, weakness of the right side of the face was observed; it spread gradually to the right arm and leg, and later to the left side so that the patient was completely paralyzed. She became idiotic and blind, and the head became very large. An operation was performed and a cyst was evacuated through an opening in the left parietal region of the skull. The patient recovered almost completely, but within a year the condition returned. At the age of 5 years a second operation was performed and the cyst was supposedly removed. Since this time the patient had been normal mentally but she was blind in the right eye and the right arm and right leg were paralyzed. At the

age of 9 years she was struck on the head by a playmate which resulted in convulsive seizures during a period of three weeks.

The present attack came on suddenly while at school. The child screamed and fell in a faint which was followed in a few minutes by right-sided convulsions. She was brought to the Los Angeles General Hospital an hour later and died soon after admittance.

Physical Examination.—The patient was somewhat obese; she was in a comatose condition and was having epileptiform seizures involving the right side of the body. The rectal temperature was 108.6 F.; the pulse rate was 140 per minute with occasional missed beats; the respiration was very irregular and of the Cheyne-Stokes type. The eyes were turned to the extreme right during the convulsions. The pupils were widely dilated, reaction to light being still present. In the left parietal region of the scalp was a large soft swelling at the site of the former operative procedures. There was also a small recent laceration of the scalp. The subcutaneous fat of the thorax and abdomen was definitely increased in amount. The reflexes of the left side were almost entirely absent. The right arm and leg twitched rapidly in an almost constant convulsion.

Gross Pathology.—There was a swelling in the left parietal region incident to a previous craniectomy. The tongue showed a recent laceration. On removal of the skull cap, a cranial defect was seen in the left parietal region. The brain was removed in its entirety, and placed in 10 per cent solution of formaldehyde U. S. P.

The hemispheres appeared asymmetrical, the left occipital and temporal regions being more prominent than the right. Over the posterior portion of the left temporal lobe was an area, about 2 cm. in diameter, which did not appear to have the usual markings of the normal cortex, but was extremely thin and semi-translucent, apparently being the wall of a cyst. At the base of the brain, lying between the optic chiasm anteriorly and the mammillary bodies posteriorly and arising from the tuber cinereum, was a small, irregular, rather firm tumor. It was about 3.5 cm. long and about 1.5 cm. thick, and extended forward along the optic tract to the chiasm, especially on the left side (fig. 11). Posteriorly it was limited by the left cerebral peduncle which it had distorted, but from which it was clearly delineated. The growth was situated in the sella turcica which it had enlarged in all dimensions, so that it was 3 cm. in length, from 2 to 3 cm. in width and 1.5 cm. deep.

On section the mass was firm and nodular. The right portion of the tumor was a dull gray, having cystic cavities varying from 1 to 5 mm. in diameter which contained a gray gelatinous substance. The cut surface showed a fine and sponge-like structure, possibly due to even smaller cystic cavities.

A transverse section through the cerebral hemispheres exposed a large cystic cavity in the left hemisphere, filling almost completely its posterior two-thirds. It was filled with a clear watery fluid. Its long axis corresponded to that of the hemisphere and measured 9 cm. In the vertical plane it was 6 cm., and in the transverse plane 7 cm. The lining of the cyst was about 0.5 mm. thick, a pale gray and almost transparent. The floor and the lateral and anterior walls of the cyst were thin and separated from the exterior of the brain by a thin lamina of gray matter of only from 3 to 4 mm. in thickness. The shape of the cavity was roughly oval, and its walls presented elevations which corresponded to the indentations of the cortical sulci. In the anteromedian aspect of the cyst was a small firm tumor nodule, which measured about 1.5 cm. in diameter; it proved to be continuous with the tumor in the floor of the third ventricle. The cyst had displaced the enlarged left ventricle toward the midline and resulted in pressure

atrophy of the basal ganglia on that side. The thalamus had almost entirely disappeared. The posterior limb of the internal capsule could not be made out. The lenticular nucleus was much smaller in size and with the caudate nucleus had been displaced anteriorly.

There was bilateral dilatation of the lateral ventricles due to the obstruction of the interventricular foramina by the tumor in the third ventricle. This dilatation was less apparent on the left owing to the compression of its cavity by the cyst. The posterior horn of the left lateral ventricle was separated from the cyst only by the very thin wall and the ependymal lining of the ventricle.

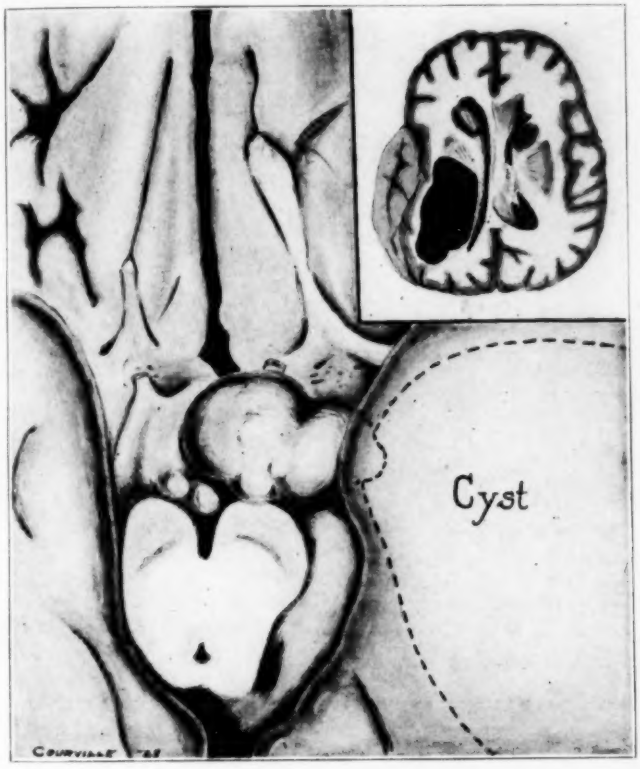

Fig. 11 (case 19).—Ganglioglioma arising from the tuber cinereum and extending into the left temporal lobe. The outline of the cyst with the mural nodule is indicated. The insert shows the size and relations of the cyst in a horizontal section through the brain.

Histopathology.—The following methods of staining were used: hematoxylin and eosin, Herxheimer's stain for fat, van Gieson's and Perdrau's methods for connective tissue, acetic acid-hematoxylin method for Nissl's granules, Bielschowsky's method for neurofibrils, Cajal's method for unmyelinated nerve fibers, Weigert's stain for myelin sheaths, the silver impregnation methods of Cajal and Schultze-Stohr for neuroblasts, the methods of Cajal, Mallory and Alzheimer for fibrillary neuroglia and Achucarro's IV variant for protoplasmic neuroglia.

Sections were taken in such a way that they showed normal tissue, tumor tissue and a portion of the wall of the cyst. In this way a check could be made

on the staining and impregnation reactions of the tumor elements and their morphology compared with those of normal structure. This does not apply to the primitive forms of the ganglion cells and glia cells for they were not found except within the limits of the tumor.

General Structure: No characteristic architecture was made out. Cells of various types were embedded in a fibrous ground substance, the larger ones being found in alveolar-like spaces (fig. 12). Areas of degeneration or hemorrhage were entirely absent, the tissue presenting a fairly uniform appearance by the various staining methods. For the most part the nature of the cellular elements and the

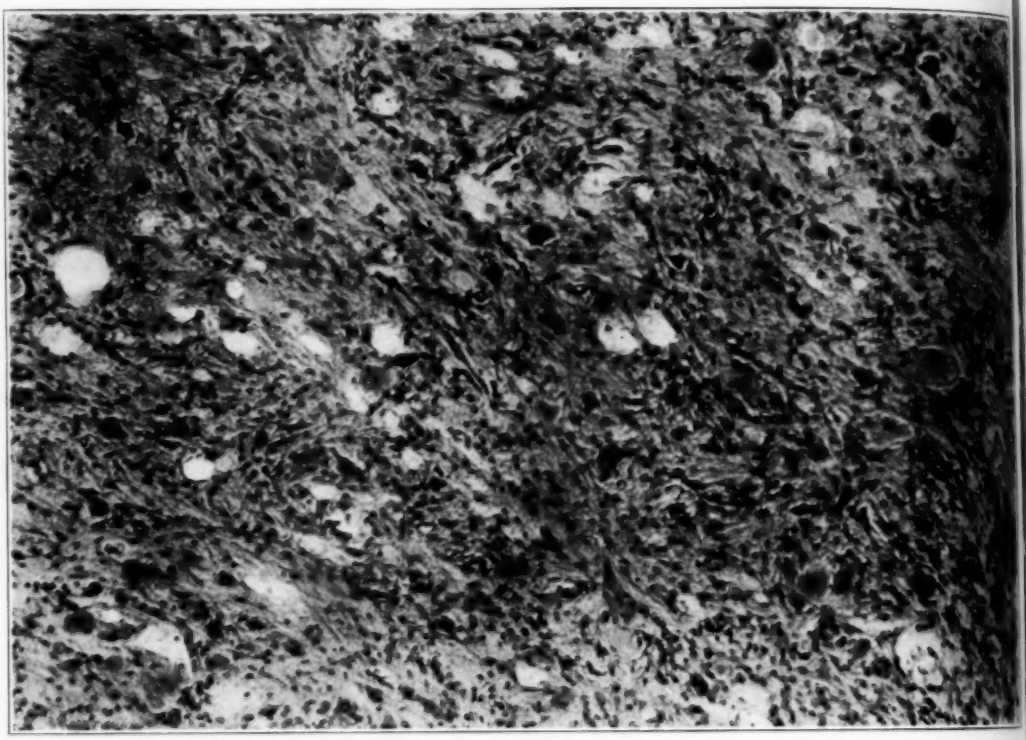

Fig. 12.—General structure of the tumor. Ganglion cells in various stages of degeneration are scattered throughout the tissue. Hematoxylin and eosin; × 200.

intercellular network was made clear only by specific methods; they will be described in their proper association.

NEURON SERIES

Neuroblasts.—Cells were scattered throughout the tumor tissue which, by the use of routine stains, appeared to be small and round with a perinuclear ring of cytoplasm. Some of the cells occurred in groups while others were more or less scattered throughout the stroma of the tumor. The methods of Cajal and Schultze-Stohr for neuroblasts demonstrated their true character. In the cell groups the morphology was especially typical. They were round or oval cells with variable

degrees of affinity for reduced silver and were evidently apolar neuroblasts, progenitors of the ganglion cells. Other cells with one or more processes probably represent unipolar, bipolar and multipolar neuroblasts (fig. 13). Neurofibrils were present in these cells which, even in the stage of the unipolar neuroblast, showed fragmentation of the individual elements. In the cell groups ("Bildungsnester" or "Proliferationzentren" of German writers) were the counterparts of the neuron through all stages of its development.

Ganglion Cells.—The morphologic characteristics of these cells were so evident, even in routine preparations, as to make their identity beyond question. They

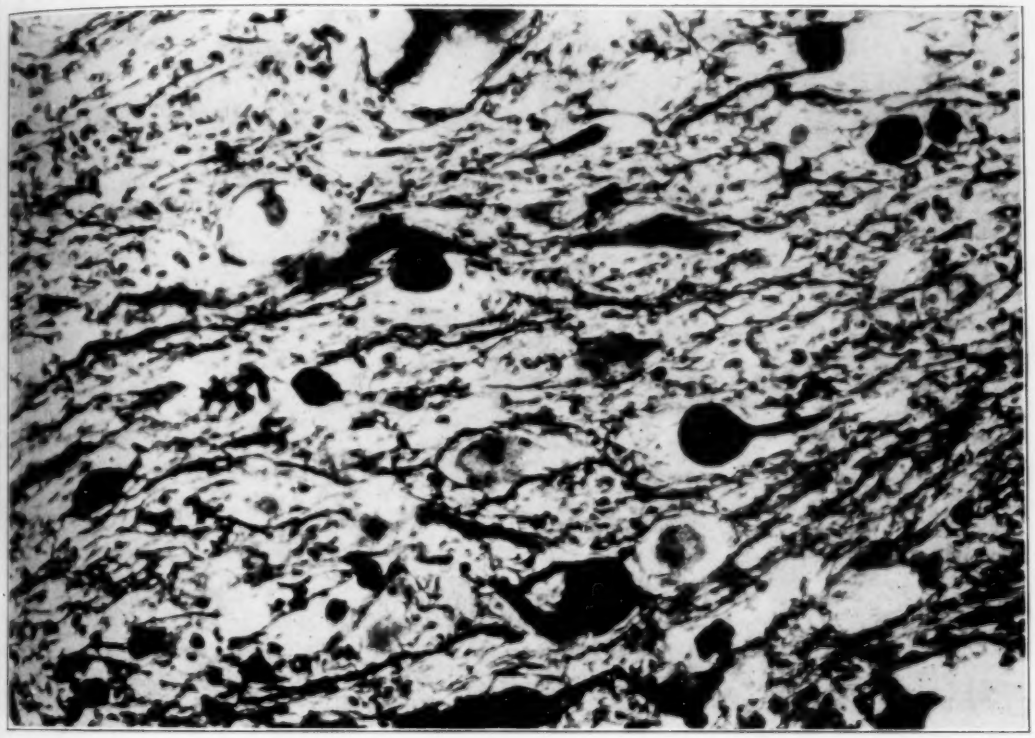

Fig. 13.—Proliferation center showing apolar, bipolar, unipolar and multipolar neuroblasts. Schultze-Stohr method for neuroblasts; × 800.

were large cells having a well defined cell body, with one or usually more processes which could be traced for some distance through the intercellular network. For the most part they were located in alveolar-like spaces in the stroma of the tumor. The cytoplasm appeared granular and specific methods demonstrated the presence of atypical Nissl's substance confined to the periphery of the cell body (fig. 14 *A*). In the more central portions about the nucleus the cytoplasm had a sort of ground glass appearance due to the dustlike remains of degenerated tigroid substance. The method of Bielschowsky for neurofibrils revealed a granular appearance of the cytoplasm similar to that described by Schmincke, who considered it to be due to broken down fibrillary substance. In rare instances one or two neurofibrils

were seen running into the larger processes of the cell (fig. 14 *B*). It is interesting to note in this connection that only a few fibrils were found in the nerve fibers of the tumor as compared with those in adjacent normal tissue. They were probably undergoing degeneration.

The nucleus of the cell was large and typically vesicular; it often assumed an eccentric position. The chromatin substance was collected into one or two round, deeply staining nucleoli, either centrally or eccentrically situated. In some cells two or even three nuclei were found, but in no instance was the number

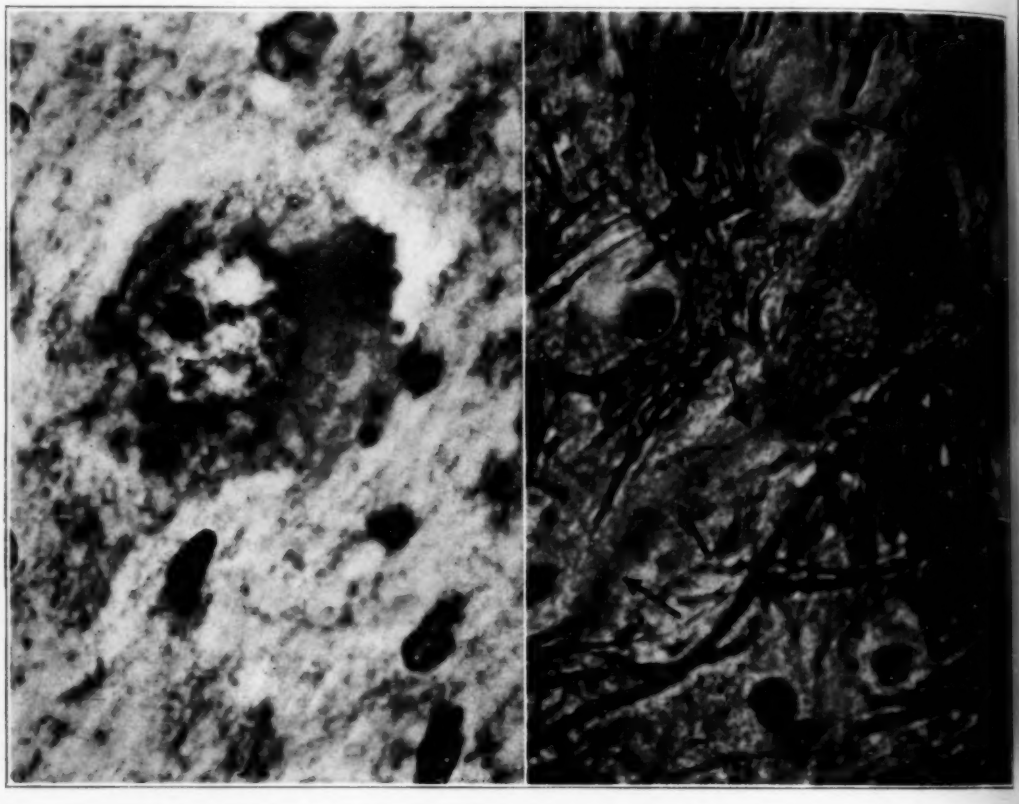

Fig. 14.—*A*, ganglion cell showing irregular distribution of the tigroid bodies. Acetic acid-hematoxylin method for Nissl's substance; reduced from × 1,000. *B*, granular degeneration of the neurofibrils. A few persisting fibrils are seen in the processes of the cell. Bielschowsky's method; reduced from × 1,000.

in a single cell as large as was described by Marinesco. The interesting inclusion forms observed by Achucarro were not observed. The nuclear membrane, which was wavy in some of the cells, tended to disappear early in the process of degeneration.

Degenerative Forms.—Regressive processes, present to a greater or lesser extent in all tumors of this type, were of interest. The earliest change apparently involved Nissl's substance and the neurofibrils. The larger chromatic granules were present

in the periphery of the cell, very much as seen in cells undergoing chromatolysis. Further changes were a granular decomposition of the cytoplasm with the loss of the cell wall, the nucleus retaining its morphologic characteristics for some time. Vacuoles of various sizes were seen in some cells, being due to a localized solution of its cytoplasm. In others degeneration seemed to be of a hyaline or amyloid nature, the cell substance becoming structureless and assuming a more or less oval shape. These so-called "corpora amylacea" stained bluish or purplish with hematoxylin and eosin, yellowish with van Gieson and pink with Mallory's stain. In other cases in which several cells were in close proximity and degenera-

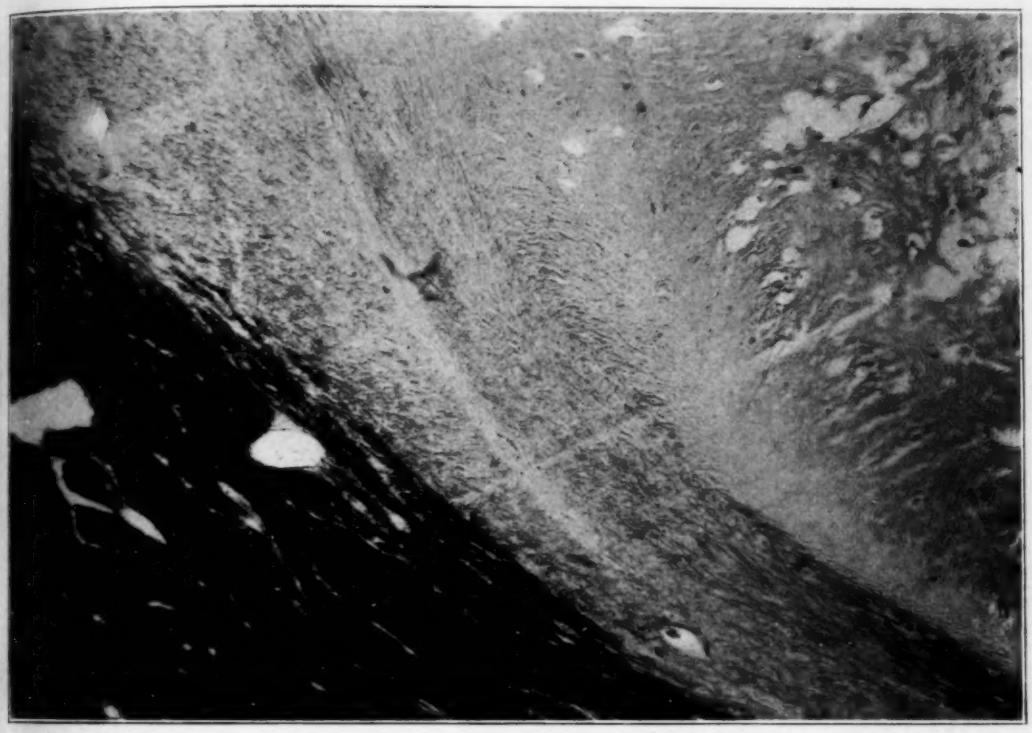

Fig. 15.—No myelinated fibers are present in the tumor in contrast to the adjacent tissue. The bundle of Vicq d'Azyr is shown in the lower left corner. Weigert's myelin sheath stain; × 95.

tion took place more rapidly, the fusion of the deteriorating cells formed large and bizzare shapes with similar staining reactions to the corpora amylacea.

Nerve Fibers.—Since the nerve fibers in the stroma of the tumor are to be considered as products of the ganglion cells, I have chosen to describe them in this connection. Cajal's method showed them to be the essential element of the intercellular network. They were unmyelinated throughout, Weigert's method not demonstrating any myelinated fibers in the tumor in contrast with the adjacent brain tissue (fig. 15). In some areas the nerve fibers ran in parallel bundles while in others they formed a tangled mass in which their individual structure

was difficult to make out. They were not uniform in caliber but in many instances had a varicose appearance. They might be straight, curved or have a zigzag course, as was observed frequently by other investigators. Many of the fibers arose from the ganglion cells or even from the more primitive forms (fig. 16). In the less dense areas of the tumors, branching occurred; it was dichotomous or at an acute angle, with the collateral running parallel to the parent fiber for some distance. In many cases the fibers formed a zone of condensation about the ganglion cells or the spaces recently occupied by them (fig. 17).

Fig. 16.—Unmyelinated nerve fibers in abundance form the major part of the stroma of the tumor. Cajal's method for unmyelinated nerve fibers; × 200.

NEUROGLIA SERIES

Spongioblasts.—Primitive forms of the supporting elements in similar tumors have been reported by previous observers. In this case, the gold sublimate method of Cajal was used, and undifferentiated forms in all stages of development have been demonstrated. It revealed something of interest which may shed light on the life history of the neuroglia. The earliest type of cell in the series was round or oval, having no processes. Such elements showed a great variation in their affinity for the gold, some being very definitely impregnated, others appearing like ghost forms (fig. 18). This suggests the possibility that the earliest differential point between the progenitors of the glia cells, on the one hand, and those

of the neurons on the other, may be of a chemical rather than of a morphologic nature. Unipolar and bipolar forms occurred together with the adult forms (fig. 19). The developing glia cells were found in proliferation centers in very much the same manner as were the neuroblasts, especially in the more central portions of the tumor. In these areas they were present in apparently equal numbers and hence played a very prominent rôle in the elaboration of the tumor.

Mallory's stain demonstrated the presence of fine bluish fibrils in the stroma of the tumor. Alzheimer's stain seemed to be more selective and showed a network of fine, reddish, wirelike fibers which formed a reticular network in the ground substance.

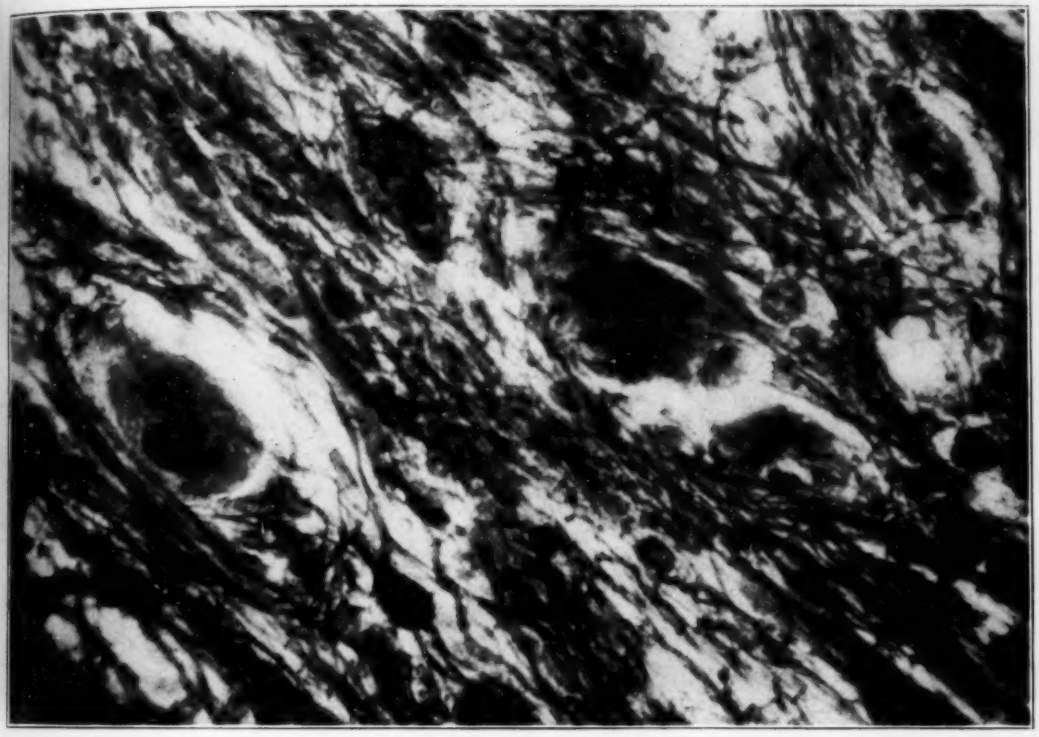

Fig. 17.—The feltwork of unmyelinated fibers about the ganglion cells is shown. Cajal's method for unmyelinated nerve fibers; × 800.

Protoplasmic astrocytes were found in that portion of the tumor which formed the wall of the cyst as shown by Achucarro's IV variant. They formed a tangled mass in some areas so that it was sometimes difficult to make out the individual cells. They may be the source of the "fusion forms" of glia described by others. This cell was found only occasionally in the central portions of the tumor.

CONNECTIVE TISSUE—VASCULAR STROMA

The blood vessels were somewhat more numerous in the tumor than in the normal brain substance, but were more irregular in size and distribution. The walls were well formed and no hemorrhages were observed. One characteristic,

which has been mentioned repeatedly by other investigators, is that of the perivascular round cell infiltration which with the specific stains showed neither a neuroblastic nor a spongioblastic character. Morphologically they resembled lymphocytes, and Marinesco attributed their presence to the elaboration of an irritative chemotactic substance by the tumor. Schmincke preferred to regard them as embryonic cells which have shown no tendency to differentiate into glia or ganglion cells. In this tumor the round cell infiltration was very marked in some regions, especially in the more central portions and where the elements

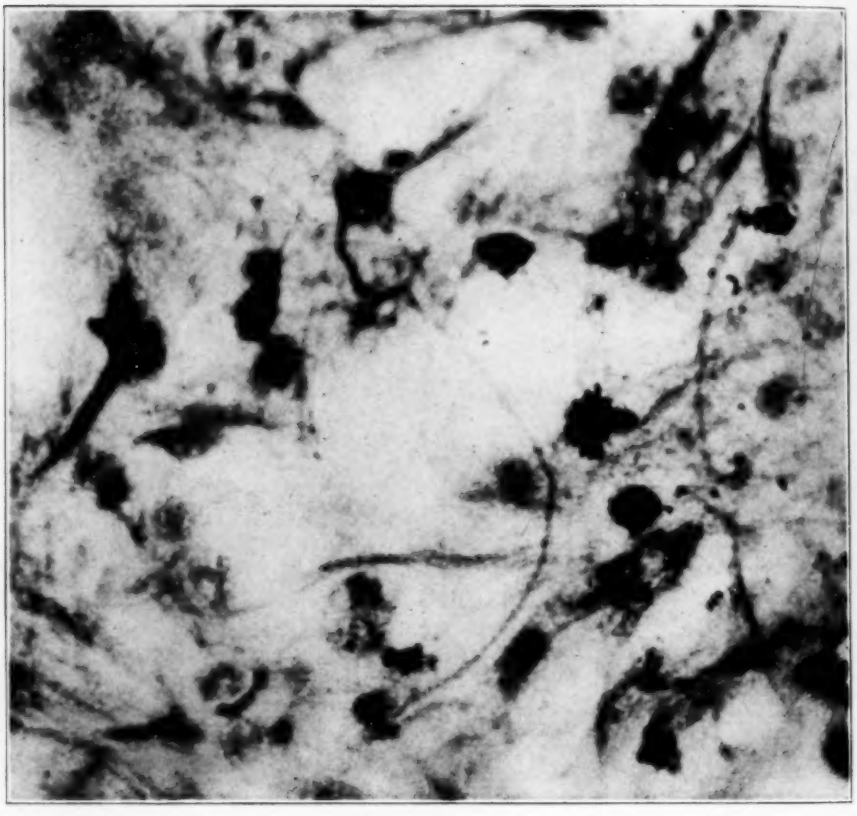

Fig. 18.—Proliferation center showing developing spongioblasts. The presence of several apolar cells is to be noted. This cell is apparently the most primitive of the series. Gold sublimate method; × 800.

seemed to have undergone pronounced degeneration. In some areas the cells were so numerous as to obscure absolutely the other constituents of the tumor. It is difficult to believe that they are immature forms of either glia or ganglion cells for this reason. It would seem as though the supposition of Marinesco, that they are the result of chemotactic substances, is a more reasonable explanation for their presence, and their occurrence in the more degenerated portions of the tumor would add weight to this argument. The connective tissue was confined chiefly to the walls of the blood vessels, and played a minor rôle in the formation

of the intercellular substance (fig. 20). A few scattered fibers could be distinguished, staining black by the method of Perdrau and red by that of van Gieson.

Fat.—When studied by the method of Herxheimer, the tissues showed a few fat globules which were located for the most part in the region of the blood vessels, in their walls or in occasional instances in the lumen itself. They were undoubtedly the products of a lipoidal degeneration which was going on in the tumor. Penfield [34] described their occurrence in gliomas and said that they indicate the phagocytic activity of the microglia in removing the products of decomposition. I was unable to demonstrate the presence of phagocytic cells by

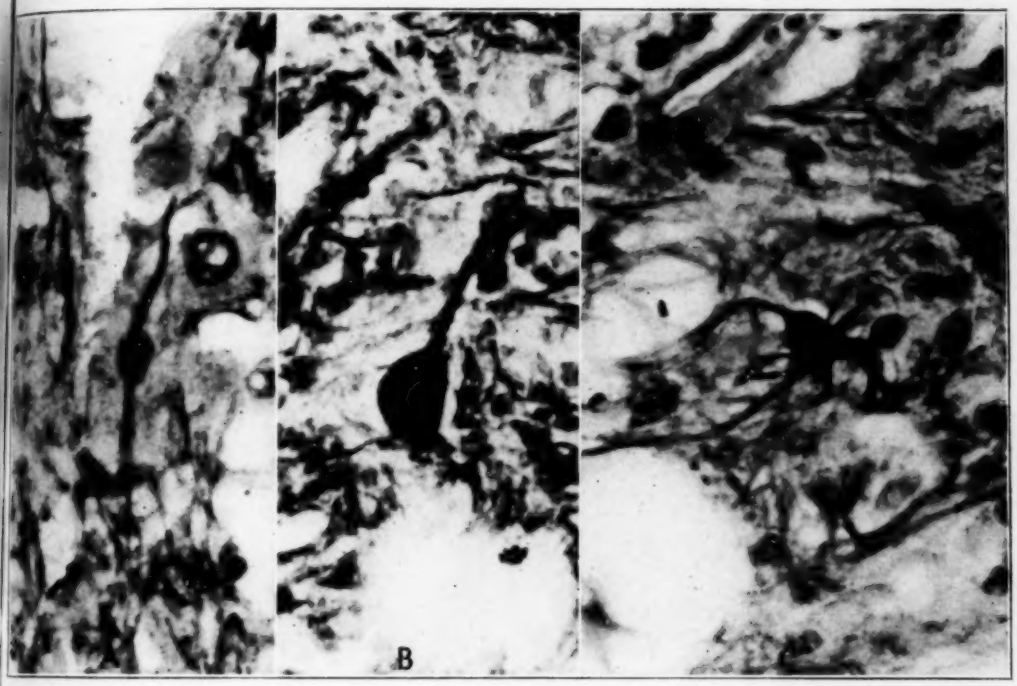

Fig. 19.—*A*, bipolar spongioblast; *B*, unipolar spongioblast; *C*, adult astrocyte. Gold sublimate method; reduced from × 1,000.

Penfield's combined method,[35] probably owing to the fact that the tissue was too old. Robertson reported that no fat was observed in his tumor.

Comment.—Because of the history of a fall in school which was associated with the convulsive attack that preceded death, an injury of the cranium was suspected. Necropsy, which was limited to the

34. Penfield, Wilder: Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77 (Jan.) 1925.

35. Penfield, Wilder: A Method of Staining Oligodendroglia and Microglia (Combined Method), Am. J. Path. **4**:153 (March) 1928.

head, instead of showing evidence of trauma, revealed the tumor and cyst previously described. A careful study of the gross characteristics of the tumor was made by the Department of Pathology at the Los Angeles General Hospital, and the specimen was preserved in formaldehyde. Because of the presence of nerve cells, the microscopic diagnosis was "neurocytoma." The exact nature of the neoplasm was discovered in the course of a routine restudy of the brain tumors in this laboratory. It belongs to that group of tumors, composed of nervous and glial

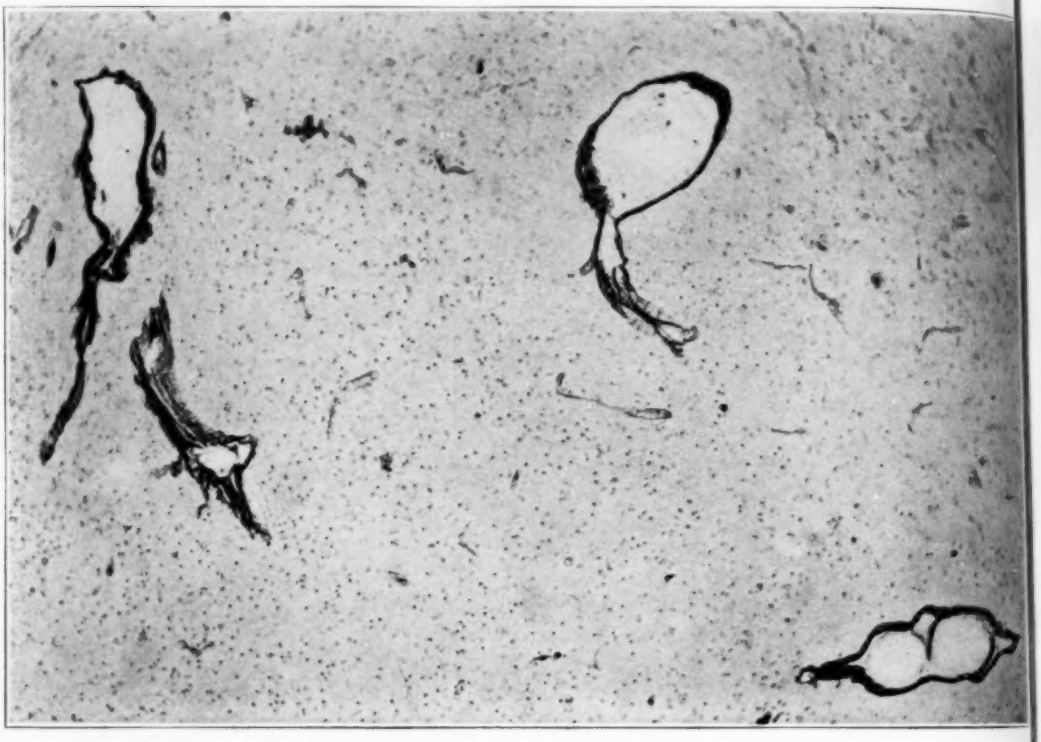

Fig. 20.—Connective tissue confined chiefly to the walls of the blood vessels. Perdrau's method; × 200.

elements, which have their origin from the tuber cinereum in the floor of the third ventricle and is the fifth case to be reported in this location. The history of the case probably coincides with the duration of life, as internal strabismus was noted at birth.

Case 20.—*A minute ganglioglioma of the tuber cinereum.*

Clinical History.—Nothing could be learned of the history in this case as the identification tag of the specimen had been lost. It was evident that the patient had died as the result of a pontile hemorrhage which had broken through into the cerebellopontile angle, forming a large clot in this situation. The tumor,

undoubtedy symptomless, was found accidentally in the course of a demonstration dissection of the brain.

Gross Pathology.—A nodule, from 1 to 2 mm. in diameter, was found in the tissue of the tuber cinereum behind and to the left of the infundibulum (fig. 21).

Histopathology.—Wishing to ascertain the true nature of the nodule and not being willing to risk its loss by cutting frozen sections, the tumor and the surrounding tissue were embedded in a paraffin block. This procedure made it difficult to use some of the metallic methods which had proved of so much value in case 19.

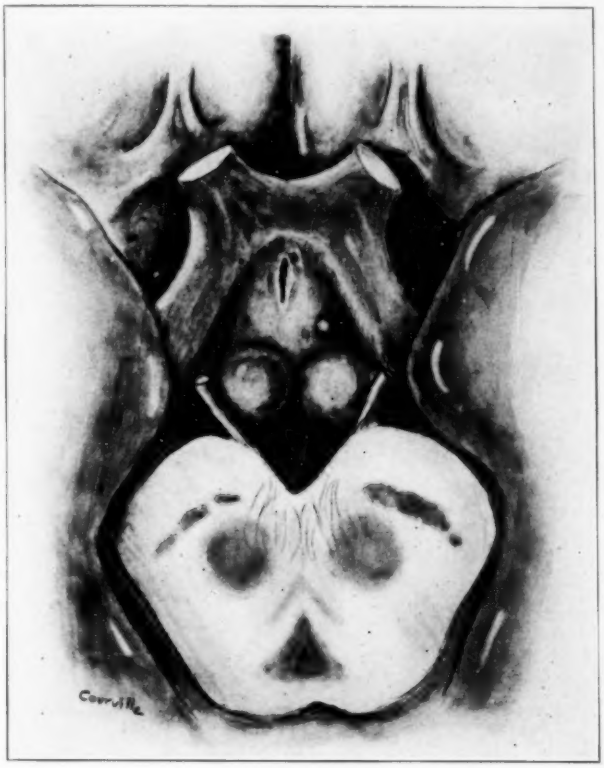

Fig. 21 (case 20).—Minute ganglioglioma of the tuber cinereum.

The methods used were: hematoxylin and eosin, Perdrau's method for connective tissue, modified gold sublimate method for astrocytes,[36] the methods of Alzheimer and Heidenhain for neuroglia fibrils, Schultze-Stohr method for neuroblasts and a modified Bielschowsky method for neurofibrils.

The tumor was easily distinguished from the surrounding tissue of the tuber cinereum by its cellularity and its well defined borders (fig. 22). Aside from the

36. As the tumor nodule was embedded in paraffin, the usual methods of metallic impregnation could not be used. With modified methods, an imperfect impregnation of the cellular elements was obtained. Further work is being done on these modifications, and, if successful, they will be made the subject of a further report.

fact that in local areas there was some tendency to be more cellular or more fibrous, as a whole the tissue was homogeneous. It consisted essentially of various types of cells embedded in a loose tissue stroma, the description of each participant being considered under their proper headings. While the tumor margin was fairly regular, it was of interest to note that in serial sections it had a tendency to extend for some distance along the larger vessels which entered the nodule. Thus radiating, tongue-like processes of neoplastic tissue were found, and the impression gained from macroscopic inspection that the tumor was perfectly round was corrected. In the central portion of the tumor and bisecting it obliquely was a slitlike

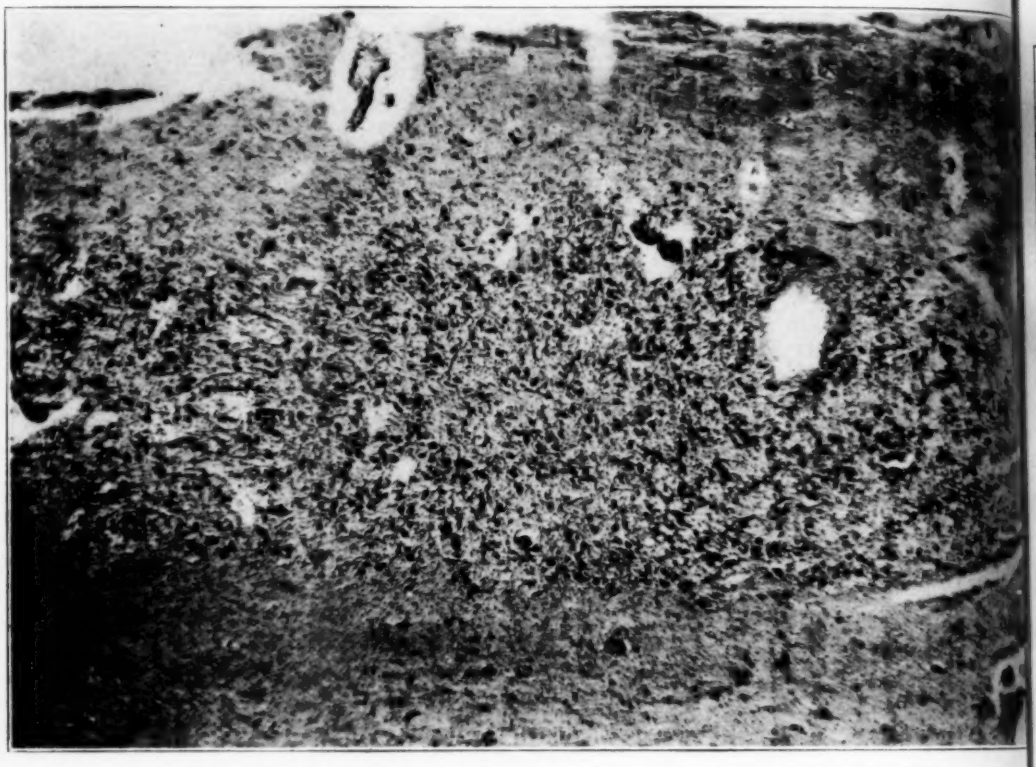

Fig. 22.—Section through the tumor nodule, showing its well defined margin. Hematoxylin and eosin; × 50.

space which extended on either side into normal tissue. The walls of the cavity seemed to be composed essentially of a condensation of glia.

Ganglion Cells.—The most conspicuous element was a large, round, unipolar or bipolar cell, situated characteristically in alveolar-like spaces in the stroma, and containing one or two large vesicular nuclei. The cytoplasm contained small granules which were unevenly distributed (fig. 23 *A*). Often, in the periphery of the cell they seemed to coalesce to form crescent-shaped masses which under higher magnification proved to be composed of globular formations. This was probably an early form of a degenerative process. A modified Bielschowsky preparation demonstrated neurofibrils occasionally in small numbers in the cytoplasm and

more often in the larger processes or nerve fibers. More typically, however, a fine black granulation was observed which probably presented degenerated fibrillary substance (fig. 23 *B*). Nerve fibers were found arising from the ganglion cells and in some instances could be traced for some distance through the tissue. They were somewhat irregular in contour, but the marked varicosity observed in other cases was not present.

The large nuclei had a well defined membrane and their chromatin content was collected into one or two round nucleoli, either centrally or eccentrically placed, with smaller condensations lying against the nuclear membrane or in the knots of the chromatin network. Not more than two nuclei were found in any of the cells.

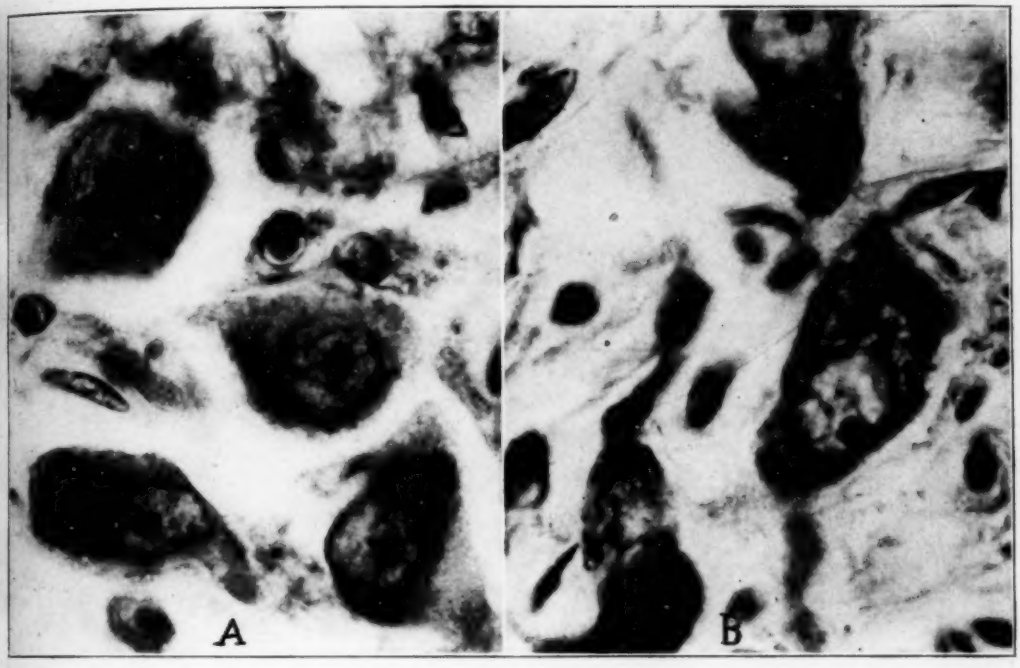

Fig. 23.—*A*, irregular granulation of the ganglion cells. Hematoxylin and eosin; reduced from × 1,500. *B*, granular degeneration of the neurofibrillae. Only traces of intact fibrillae are to be seen. Modified Bielschowsky.

"Twin cells" were occasionally observed, apparently having just completed the process of direct cell division. No mitotic figures were observed, nor could any of the transitional forms described by other writers be found.

In addition to the degenerative changes described, one or two other points should be mentioned. In some cells, a loss of the cell wall and the nuclear membrane in certain areas seemed to indicate that degeneration had begun. In such instances the nucleus assumed an eccentric position in the cell, and irregular distribution of the granulation of the cytoplasm was a frequent attendant observation. In other cells that had not lost the characteristic markings larger, black, round globules were noted. These did not have any particular situation in the cell but were scattered throughout the cytoplasm.

The Schultze-Stohr method revealed smaller cells which were either unipolar or bipolar and were probably neuroblasts. They were but few in number as compared with the adult cells or with the primitive forms observed in case 19. With the hematoxylin and eosin stain, this cell appeared as an intermediately sized unipolar or bipolar cell with dark cytoplasm, and the nucleus resembled those of the ganglion cells.

Glia Cells.—The methods of Alzheimer and Heidenhain demonstrated the presence of large numbers of glia fibers which formed a filigree network in the tumor stroma (fig. 24 *A*). With the many capillaries, these fibers formed by far

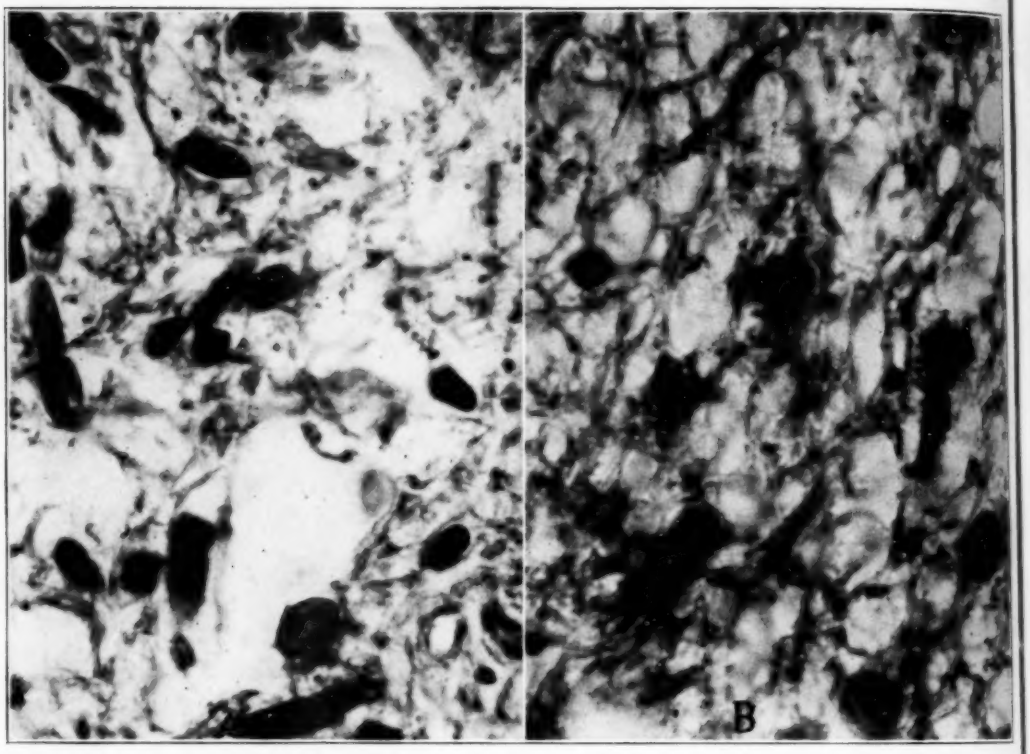

Fig. 24.—*A*, filigree network of glia fibers. Heidenhain method for glia fibrillae; reduced from × 1,350. *B*, traces of glia fibers can be seen in relation to the cell body. Modified gold sublimate method; reduced from × 1,350.

the greater part of the intercellular substance. They had their origin apparently from nuclei with a well defined membrane and an evenly distributed chromatin content, evidently fibrillary astrocytes. A modified gold sublimate method seemed to confirm this impression. The cell bodies in this preparation, while not as definitely outlined as in impregnated frozen sections, were recognizable from their morphology, fibrils being detected in some of the cells (fig. 24 *B*). Binucleated cells were found occasionally which suggested either amitotic cell division of the astrocytes or fusion forms. Embryonic elements were not observed, although judging from the presence of similar but smaller cells they may have been present.

There was a rich capillary network in the tumor which was clearly seen in all preparations. The vessels were composed only of endothelium, the oval or spindle-shaped nuclei being clearly demonstrated. Connective tissue, as shown by the method of Perdrau, was confined entirely to the walls of the larger blood vessels. The perivascular round cell infiltration so frequently mentioned by other observers was not found.

Comment.—The tumor was undoubtedly too small to give rise to any symptoms. The occurrence of binucleated cell forms, the morphology of the contained structures, the tendency to grow along the blood vessels and finally the occurrence of primitive neuroblasts are strong evidences of a neoplastic character. It is to be regretted that the size precluded a more accurate study by metallic methods, for could

TABLE 1.—*Gangliogliomas of the Central Nervous System*

Case	Author	Year	Age	Sex	Location of Tumor	Duration of Symptoms
1	Worcester	1901	42	M	Left parietal lobe	3 years
2	Dumas	1904	29	F	Right cerebral hemisphere	About 1 year
3	Schmincke	1911	17	M	Right temporal lobe	9 years
4	Pick and Bielschowsky	1911	24	F	Cervical cord and medulla	?
5	Achucarro	1913	20	M	Cerebellum	2 years
6	Schmincke	1914	17	M	Right temporal lobe	?
7	Robertson	1915	16	F	Tuber cinereum	About 1 year
8	Berblinger	1917	17	F	Septum pellucidum	?
9	Greenfield	1918	26	F	Tuber cinereum	About 3 years
10	Olivecrona (case 10)	1919	39	M	Right parietal lobe	8 days
11	Olivecrona (case 11)	1919	?	F	Right frontal lobe	?
12	Lhermitte and Duclos	1920	36	M	Left cerebellar hemisphere	1 year
13	Bielschowsky	1925	26	M	Multiple tumors	15 years ?
14	Perkins	1926	16	M	Floor third ventricle	3 weeks
15	Marinesco	1926	40	F	Tuber cinereum	?
16	Horrax and Bailey	1928	40	M	Pineal body	15 months
17	Bielschowsky and Henneberg (case 17)	1928	16	F	Left temporal lobe	11 years
18	Bielschowsky and Henneberg (case 18)	1928	11	F	Right temporal lobe	7 years
19	Courville (case 19)	1928	15	F	Tuber cinereum	Life ?
20	Courville (case 20)	1928	?	?	Miliary nodule in tuber cinereum	?

this have been done, the final proof, the presence of immature glia cells, might have been established conclusively. The benign nature of the tumor is suggested by its small size, the infrequency of immature cells, the clearly defined margin, the absence of mitotic figures and the presence of amitotic cell division.

PATHOLOGIC ANATOMY

It becomes evident from a study of this series of cases that gangliogliomas in the central nervous system are usually small, firm, fairly well delineated tumors which may be found in almost any situation in the brain or cord. They are usually single, although in two cases they were multiple (Greenfield, Bielschowsky). They are not truly invasive and are therefore benign. Case 6 (Schmincke) showed concentric rings in the brain substance surrounding the tumor, indicating its expansive growth. The color of the tumor varies, being yellowish gray

or grayish white in some cases and purplish in others. On section the tumor is firm and fibrous and may show small cysts in various regions giving it a spongy appearance. Case 6 showed small punctate hemorrhages, an observation which, with the exception of that of Berblinger, has no counterpart in any of the other cases reported in the central nervous system. The case presented by Lhermitte and Duclos is of interest in that the new growth had the appearance of a diffuse hypertrophy of the cerebellar cortex. The lesions are characterized structurally by their comparative freedom from extensive degenerative changes. Perhaps the only evidence of such changes is the presence of small cysts in the substance of the tumor as observed on section. Their formation seems to be fairly definite in the tumor which I have studied. It is clear that the ganglion cells occupy small alveolar-like spaces in the meshes of the nerve fibers. As the result of degenerative changes in these cells, these spaces may become filled with a gelatinous substance and if several such spaces should coalesce the space becomes macroscopic and its contents appear as a grayish semitranslucent droplet of rubbery consistency. This process could be traced definitely in the tissues of the tumor. If the process were slower it would probably result in the formation of the so-called "corpora amylacea" described by other writers, or even of the calcified masses found in the cases of Perkins and of Bielschowsky.

The cause of the formation of the large cysts is not so easily established. These cysts were found in the cases of Worcester, Bielschowsky and Henneberg and in case 19. They were filled with clear watery fluid and had a nodule of the tumor protruding into the cavity from the wall. In this respect they resemble the large cysts associated with the astrocytomas, except that the content of the latter is usually a yellow coagulable fluid. It may be that in these two cases some primitive cells were present which were capable of secretion. In case 19, the portion of the tumor bordering the cyst showed a layer of cells probably having a very primitive nature without any demonstrated morphology by any of the specific stains. The balance of the cyst wall was smooth and was underlined by a condensation of glial tissue.

Histopathology.—It becomes evident in the microscopic study of the tumor tissue with the aid of specific methods that this is a new growth, the cellular constituents of which have a common origin in a primitive type of cell. This is shown clearly by the various types of neuroblasts in the developing nests revealed by reduced silver. Developing glial elements are also shown clearly by the gold sublimate method. The cells from which both arise seem to be small apolar lymphocyte-like cells, and the earliest change seems to be a chemical rather than a morphologic one as manifested by the attraction by the cell for either

gold or silver. Thus in the cell groups there are small round cells with a very small amount of cytoplasm which are slightly impregnated with one or the other of the two metals, indicating the progenitor of the ganglion cells or glia cells.

It is interesting in this connection to compare this tumor with the "medulloblastoma" of Bailey and Cushing from the standpoint of the cell of origin and the course of its development. The latter is found

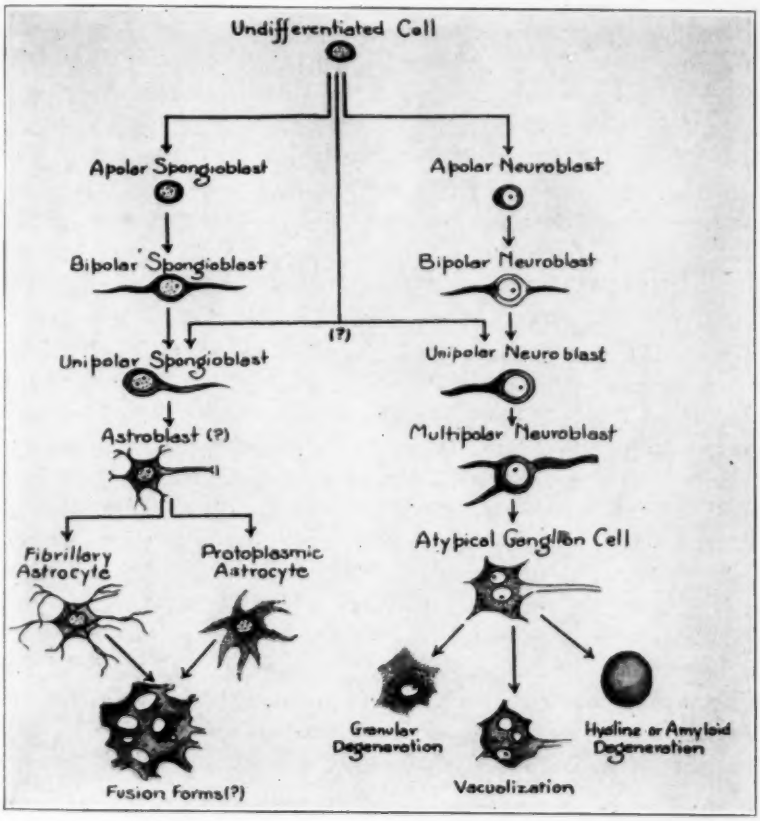

Fig. 25.—Development of the ganglionic and glial elements, as demonstrated by the cell types found in the tumor. The formation of unipolar neuroblasts and spongioblasts from indifferent cells (medulloblasts) without passing through the intermediate stages could not be made out. Astroblasts were not found in recognizable form, although atypical or transitional forms may have been present.

commonly in the midline of the cerebellum during childhood and is considered to be derived from the carrot-shaped medulloblasts or indifferent cells. They have been observed to develop into unipolar neuroblasts or spongioblasts when studied with specific methods. The ganglioglioma likewise develops in the direction of both ganglionic and glial

elements, the differentiation proceeding through all stages to the adult type of cell (fig. 25). It has for its origin, however, the small apolar cell which apparently has no resemblance to the medulloblast. Its counterpart may be the small round cells which metastasize from the parent to the spinal subarachnoid space. The malignancy of these two types of tumors, like those of epithelial origin, depends on the degree of differentiation of the constituent elements. In the case of medulloblastomas complete differentiation occurs rarely, if ever, while in the ganglioglioma it seems to be the rule.

Judging from the descriptions of previous observers and from observations in my cases, the most conspicuous element is the ganglion cell, for it is present in greater numbers than other types. The quantitative relationship of these two formative elements has not been discussed by most writers. Bielschowsky, in his second case, mentioned that this ratio varies in various tumors.

GANGLIOGLIOMA OF THE INFUNDIBULAR REGION

From the review of the literature it is evident that for tumors of this group in the brain and cord, the most common situation is the tuber cinereum forming the floor of the third ventricle (cases of Robertson, Greenfield, Perkins, Marinesco and my own). Its greater frequency in this region probably has a definite relationship to the embryonic development of this portion of the brain. Perhaps in no other situation, unless it is the roof of the fourth ventricle, does the brain retain its primitive state so completely throughout its formation period. It is not at all improbable that these tumors arise from the inactive cells of the original basal plate which do not have a definite function. These were found to be numerous in the tissues of the tuber cinereum surrounding the tumor in case 20. The essential facts relating to this group of cases have been summarized in condensed form in table 2. While the average age of the patients is 22⅓ years (owing to the age of 40 in the case of Marinesco), this tumor tends to occur during adolescence and early adult life. Four of the five cases were found in females. The duration of the symptoms varied from three weeks to probably the lifetime of the patient. The essential reason for the wide variation in the duration of the symptoms is to be found in the anatomic relationships of the tumor. With the exception of the enlargement of the sella and consequent pressure atrophy of the pituitary gland, the tumor may grow without any marked clinical disturbance. If, however, it should suddenly obstruct the interventricular foramina, acute hydrocephalus would result. This, without doubt, is the explanation of the acute symptoms with a fatal termination which have been observed in most of the cases (Robertson, Marinesco, Perkins and my own). The

motor symptoms observed in the cases of Robertson, Marinesco, Perkins and myself are most certainly due to backward pressure of the tumor on the motor pathways in the basis pedunculi of the mesencephalon, which is borne out by a study of my cases. Lateral extension would involve the optic tracts, resulting in hemianopia, bitemporal if expand-

TABLE 2.—*Gangliogliomas Arising from the Tuber Cinereum*

Case	Age; Sex*	Gross Pathology	Pressure Symptoms	Symptoms of Contiguous Parts	Pituitary Symptoms	Duration of Symptoms
Robertson, 1914	16 ♀	Firm, plum-sized tumor between legs of optic chiasm; enlargement of sella turcica	Headache; failing vision;† vomiting (2 times)	Right hemiparesis; right hemianesthesia; right paresthesias	Abdominal adiposity	About 15 months
Greenfield, 1919	26 ♀	Tumor 9 by 5 by 4.5 cm. arising from tuber cinereum; also multiple nodules from base of brain; pituitary gland not found	Headaches; failing vision†	.....	Enlargement of cranial bones, hands and feet; separation of teeth; pigmentation of skin of axillae and abdomen	About 2½ years
Marinesco, 1926	40 ♀	Tumor size of pigeon's egg in infundibular region and adherent to left hippocampal convolution	Terminal coma	Epileptiform convulsions†		
Perkins, 1926	16 ♂	Firm purple tumor, 3 by 4 by 2.5 cm., arising from the floor of the third ventricle; calcification present	Headache; vomiting drowsiness; failing vision;† died in coma	.....	.....	About 3 weeks
Courville, 1928	15 ♀	Tumor, 3.5 by 1.5 by 2 cm., in region of the tuber cinereum, associated with large cyst in the left cerebral hemisphere	Enlargement of the skull; failing vision;† died in coma	Internal squint; right-sided weakness to complete hemiplegia, with recovery after drainage of cyst; right-sided jacksonian convulsions	Child very obese	Probably throughout course of life
Courville, 1928	..	Small nodule, about 2 mm. in diameter, posterior and to right of infundibulum				

* ♀ indicates female, and ♂, male.

† These symptoms may belong to another group; the history is not specific.

ing equally on both sides or homonymous if entirely to one side, providing, of course, that the changes incident to acute hydrocephalus had not previously obscured vision. This seems to be the rule, for hemianopia has not been recorded in any instance, although complete histories are not available in all cases. Pressure on the hippocampal and uncinate

gyri could be the source of olfactory and gustatory hallucinations in the same manner as observed in extensions of pituitary tumors.[37] Such have not been recorded.

The symptoms, then, that might be present in tumors arising from the floor of the third ventricle, may be divided into three groups: (1) those due to increased intracranial pressure, (2) those due to local extension of the tumor and (3) those due to pressure atrophy of the pituitary gland. Symptoms of the first group are the same as would be present in other cases of increased pressure, such as headache, vomiting and choked disk. The sudden onset of such symptoms, if recognized as a syndrome of intracranial pressure, might be interpreted as having a mechanical basis. Local extension of the tumor, as already outlined, would give rise to optic signs and symptoms, hallucinations of smell and taste and motor disturbances. Pressure atrophy of the pituitary gland would give rise to hypofunction perhaps of mild degree, manifested by adiposity and diminished activity of the sex glands (as seen in the cases of Robertson, Perkins and myself). It is a remarkable coincidence that in the case of Greenfield there was a typical clinical picture of acromegaly. It must have been due to a coincident chromophil adenoma of the pituitary gland the presence of which could not be verified because at autopsy no trace of the pituitary could be found.

It is possible that this tumor might be confused with "tumors of the pituitary group." The enlarged sella and possible calcification (Perkins' case), as shown by the roentgenogram, together with evidences of hypopituitarism would suggest a calcified adenoma or a craniopharyngeal pouch cyst. The age of the patient and symptoms of increased intracranial pressure would be in favor of the latter diagnosis. It is doubtful whether an antemortem diagnosis will ever be made, unless the tumor is removed at an operation, because of the rarity of the lesion and the confusion of the clinical syndrome with that of other and more common tumors.

SUMMARY AND CONCLUSIONS

1. About seventy cases of the commonly called ganglioneuroma have been reported in the literature. Of this number, eighteen have occurred in the tissues of the central nervous system. These are located as follows: one in the frontal lobe, two in the parietal lobe, one possibly in the occipital lobe, four in the temporal lobe, one arising from the septum pellucidum, four from the tuber cinereum, one from the pineal body, two in the cerebellum, one in the cervical cord and medulla, and in one case there were multiple tumors. A brief summary of these cases is given.

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37. Cushing, Harvey: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912, p. 246.

2. To this list of cases involving the central nervous system, I have added two, both of which had their origin in the tissues of the tuber cinereum. One was a fairly large tumor found in a girl, aged 15, and was associated with a large cyst in the left cerebral hemisphere. It had apparently caused symptoms throughout the life of the patient. The other tumor was a minute nodule, found accidentally in the course of a routine demonstration dissection of the brain, and was undoubtedly symptomless.

3. These tumors have a fairly definite composition, being composed of primitive and adult forms of both nerve cells and glia cells which can be demonstrated by the use of specific methods of staining. The earliest form of cell seems to be a small apolar element which is capable of developing into either supporting or functional types. The first indication of the direction of its differentiation seems to be chemical rather than morphologic—an affinity for either gold or silver. By the metallic methods all stages in the process of differentiation have been demonstrated.

4. Many names have been applied to the tumor. Because of the presence of both ganglion cells and neuroglia, the name ganglioglioma is suggested as being descriptive and direct. The presence of nerve fibers in the tumor is not included in the name because it is now accepted by all that they are an integral part of the ganglion cell and not the result of the proliferation of sheath cells. If this is true the addition of "neuroma" to the term is redundant. For tumors of the peripheral nervous system in which sheath cells are present instead of neuroglia, the term ganglioneurinoma may be considered.

5. From their histologic structure it would seem as though the tumor must have origin in the retarded development of undifferentiated (indifferent) cells early in the formative period. Under some unknown stimulation these cells assume a neoplastic nature and progress through the stages which lead to the adult form of cell. The presence of adult ganglion cells and astrocytes indicates that differentiation has been complete, and therefore the tumor must be essentially benign.

6. A study of the larger group, those arising from the tissues of the tuber cinereum, is made. From the nature of the constituent elements of this region it is logical to believe that the tumor may have origin in the indifferent cells of the basal plate of the diencephalon which in any case retain a primitive state. This is shown by the occurrence of small nerve cells in this location which apparently are functionless.

THE REACTION OF THE CENTRAL NERVOUS SYSTEM TO EXPERIMENTAL UREA INTOXICATION *

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The reaction of the microglia to wounds, tumors, softenings and other destructive processes is well known. Its conversion into rod cells and compound granular cells has been demonstrated beyond a doubt by Hortega. In infections, such as dementia paralytica, the metamorphosis is into rod cells, whereas in frankly destructive processes, such as cerebral softenings and wounds, the response of the microglia consists in a rapid and widespread conversion into compound granular corpuscles. In the former instance the result is a generalized microgliosis, whereas in the latter the microglia cells act as phagocytes to remove the products of destruction and disintegration (Hortega;[1] Hortega and Penfield[2]). The reaction of these cells, however, to toxic processes which are not frankly destructive is not clear, though scattered observations have been recorded. It is of interest to know, therefore, whether intoxications produce a change in the microglia, and if so, the nature of the change.

On the other hand, the reaction of the astrocytic neuroglia and oligodendroglia to toxic and toxic-infectious processes has been well studied. Hortega[3] and others have demonstrated the formation of ameboid cells in such states, derived chiefly from the astrocytic neuroglia but contributed to in part by the oligodendroglia. The reaction of oligodendroglia to toxic processes by an acute swelling has been described by Penfield and Cone.[4] Despite knowledge of the reaction of the neuroglia in these toxic states, it is of interest to study its reaction in experimental uremic poisoning, in order to view the simultaneous reaction of the neuroglia and the microglia.

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* From the Laboratorio de Histologia Normal y Pathologica, Madrid, Professor P. del Rio-Hortega, Director.

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2. Del Rio-Hortega, P., and Penfield, W.: Cerebral Cicatrix, Bull. Johns Hopkins Hosp. **41**:278, 1927.

3. Del Rio-Hortega, P.: Sobre la verdadera significacion de las celulas neuroglicas llamada amiboides, Bol. Soc. españ. de Biol. **8**:229, 1918-1929.

4. Penfield, W., and Cone, W.: Acute Swelling of Oligodendroglia, Arch. Neurol. & Psychiat. **16**:131 (Aug.) 1926.

MATERIALS AND TECHNIC

Rabbits were employed in the investigation, and injections were made with pure urea. In the first series of animals the urea was injected subcutaneously in doses of from 1 to 2 Gm. a day. The total dosage varied from 16.25 to 37.25 and 53.25 Gm. of urea. Animals were killed at various stages of experimentation in order to determine the reaction of the nerve elements to short and prolonged intoxications. On the whole, the resultant intoxications in subcutaneous administration were deep, but in order to produce more profound effects, intravenous injections with urea, as well as with human urine, were made into another series of animals. With the combined administration of urine and urea intravenously, the resultant intoxications were profound. The reactions of the animals were variable, some exhibiting loss of appetite and weight after small doses and others resisting intravenous administration of large doses of urine and urea.

All tissues were fixed in formaldehyde-bromide, formaldehyde and alcohol immediately after the animal was killed. The silver carbonate method of staining for microglia, neuroglia and nerve fibers was employed, in addition to the gold-sublimate method of Cajal and the toluidine blue technic for the demonstration of nerve elements. All portions of the nervous system, including the spinal cord, were investigated.

PATHOLOGIC CHANGES OBSERVED

Three of eight animals given injections showed mild changes in the nervous system, and one gave evidence of a severe intoxication. In every instance in which evidence of injury was present, the cerebral white matter was more severely injured than the gray. The cortex, however, though mildly involved, was nevertheless universally implicated. This predominant involvement of the white as compared with the gray matter, constitutes one of the most interesting and striking features in the investigation.

Microglia.—The microglia in all but one case showed no evidence of reaction to the intoxication, even in instances with marked clinical evidences of toxicity. Occasional hypertrophic forms were found here and there, evidenced by a thickening of the processes and a loss of the spinous projections together with a retraction of the prolongations. These minor changes, present here and there in every case, were entirely insignificant however. In the one case with severe cerebral injury, the microglia showed definite changes. Here, too, the pathologic change was much more marked in the white than in the gray matter. The microglia in the cortex was much better preserved than in the white matter, where the pathologic process involved all the microglia cells more severely than in the gray substance. The type of change observed may be seen in figures 1 and 2. The nucleus was markedly pyknotic and often shrunken. The processes were generally hypertrophied and often flexuous and tortuous, presenting a wiry appearance. The most striking

feature, however, was the swellings, which may be seen scattered along the processes at frequent intervals. These were fusiform or nodular, the former appearing like a localized dilatation of the process and the latter like a sort of fungus attached to the prolongation. Often these swellings were visible at the bifurcation of a process, as in the normal condition, but in most instances they were found either at the end of a prolongation or somewhere along its course. Sometimes the microglia

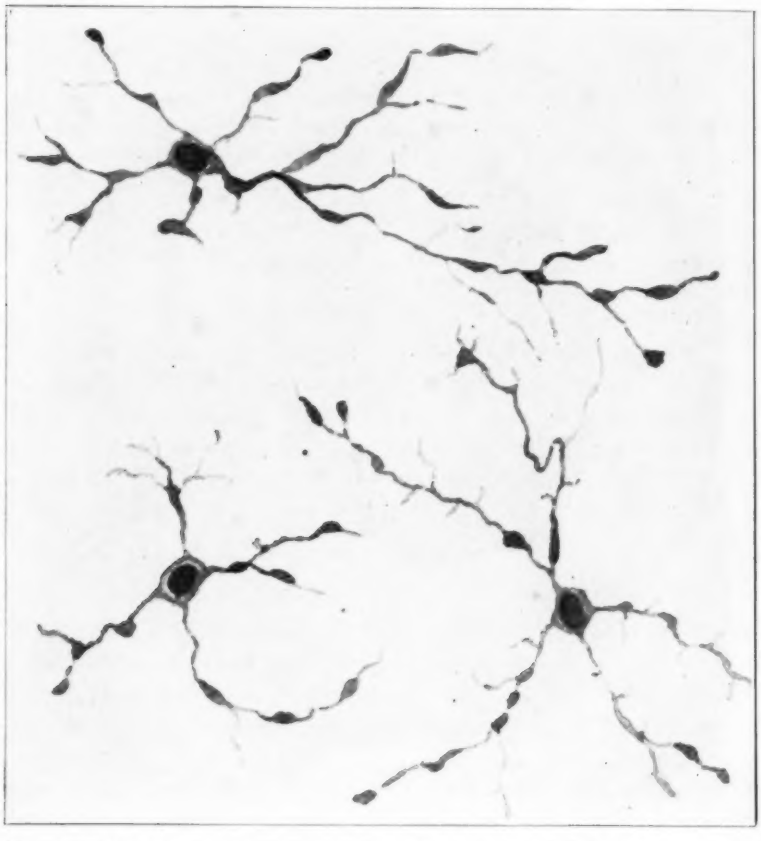

Fig. 1.—Microglia showing numerous nodosities, hypertrophy of the processes and pyknosis of the nucleus; silver carbonate stain of del Rio-Hortega.

was seen in lamellar forms around the vessels. No outspoken rod-cell formation was noted, but transition forms with loss of the rich arborization of the normal cell could be seen. In figure 2 can be seen the transformation of a microglia cell into a rod cell. In the development of the latter there is a progressive decrease in the number of processes until at length only a few stream out from the cell in a bipolar arrangement.

Neuroglia.—Of all the elements in the nervous system the fibrous astrocytes and the perivascular neuroglia in the white matter showed the greatest amount of injury. The protoplasmic astrocytes in the gray substance remained relatively intact even in the severe cases of intoxication, but many of these cells in connection with the vessels showed evidence of disease. In three cases of mild intoxication the fibrous astrocytes showed a slight evidence of hypertrophy. The type of change is characterized by a slight swelling of the cell body and a definite hypertrophy of the prolongations. Occasionally a flexuosity of the processes

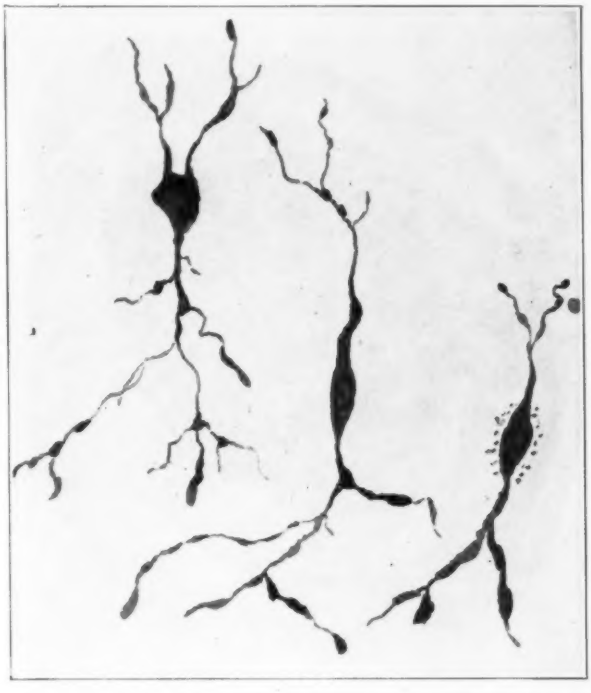

Fig. 2.—Microglia showing the development of rod cells, with a progressive loss and hypertrophy of the prolongations; silver carbonate stain of del Rio-Hortega.

could be seen, with a curling and tortuosity of the fibrils of Ranvier-Weigert in the cell body. Such changes in the milder cases of intoxication were not universally present in the fibrous astrocytes, but nevertheless were frequent. In the severe case of intoxication the fibrous neuroglia cells were universally and severely diseased. All were in one stage or another of clasmatodendrosis and of forming ameboid cells. Figure 3 shows the various types of pre-ameboid and ameboid cells being formed by the fibrous astrocytes, and figures 4, 5 and 6 demonstrate

these cells grouped around vessels. The formation of ameboid cells has been well studied by numerous investigators. Early in the transformation of the fibrous neuroglia into ameboid cells there is a retraction and shrinking of the nucleus with some pyknosis, accompanied by a swelling of the processes. These are swollen several times beyond their normal size, often with bulbous terminations, seen in figures 3*B* and 3*C* in the pre-ameboid stage. The cytoplasm simultaneously becomes

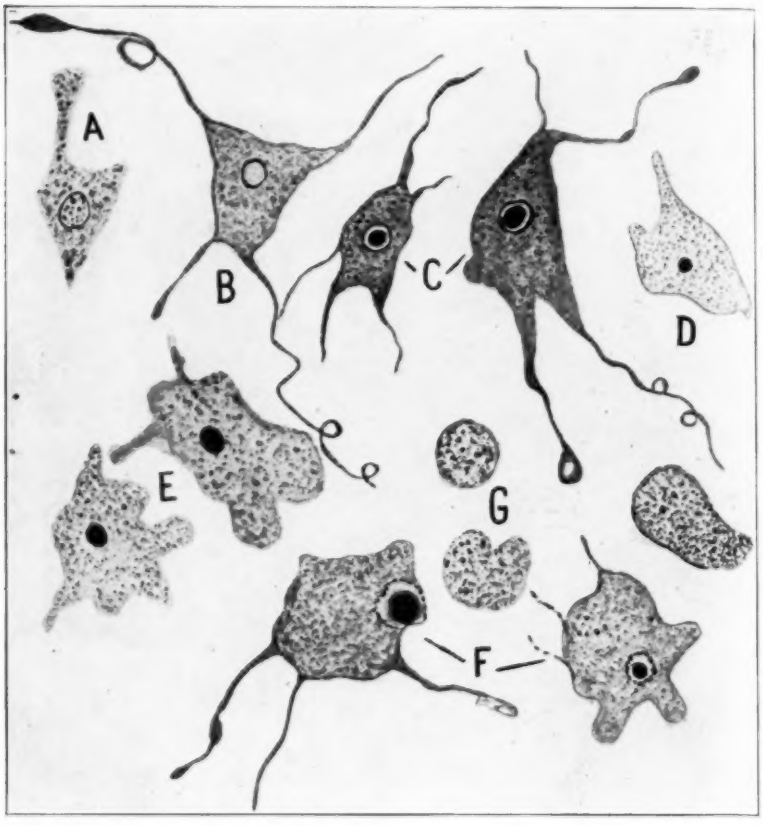

Fig. 3.—Astrocytic neuroglia in various stages of development into ameboid cells. *B*, *C* and *D* represent pre-ameboid cells with flexuous prolongations. *E* and *F* are transition forms between ameboid and pre-ameboid cells: silver carbonate stain of del Rio-Hortega.

swollen and assumes a granular appearance. Later, the prolongations become shorter and more stubby, giving the cell a true ameboid appearance (fig. 3*E* and 3*F*), and the cytoplasmic structure becomes finely granular and pulverized and finally homogeneous. Finally, the stubby prolongations are lost entirely, and the ameboid cells are seen as oval,

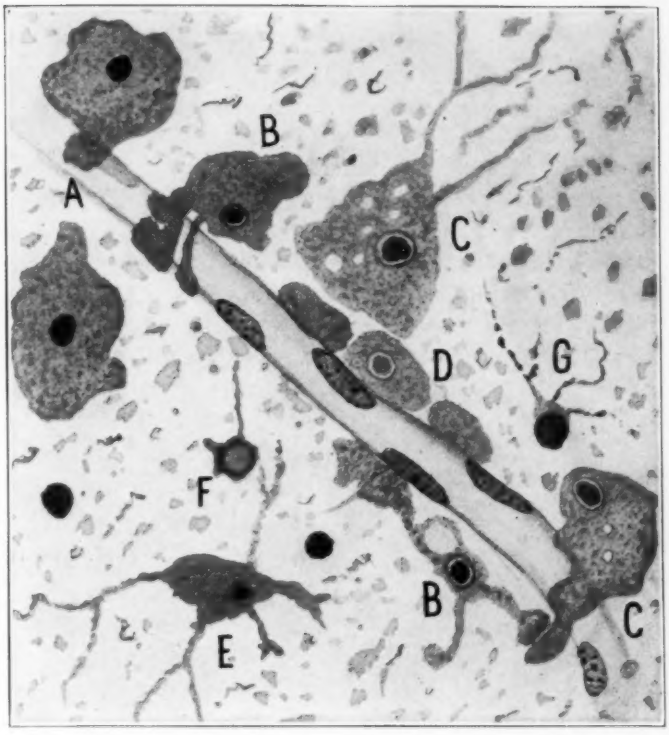

Fig. 4.—A group of pre-ameboid cells around a vessel. The cells at *B* show markedly swollen vascular processes and feet. *C* shows a pre-ameboid cell just before loss of the processes. *D* shows an ameboid cell. *F* and *G* are oligodendroglia; silver carbonate stain of del Rio-Hortega.

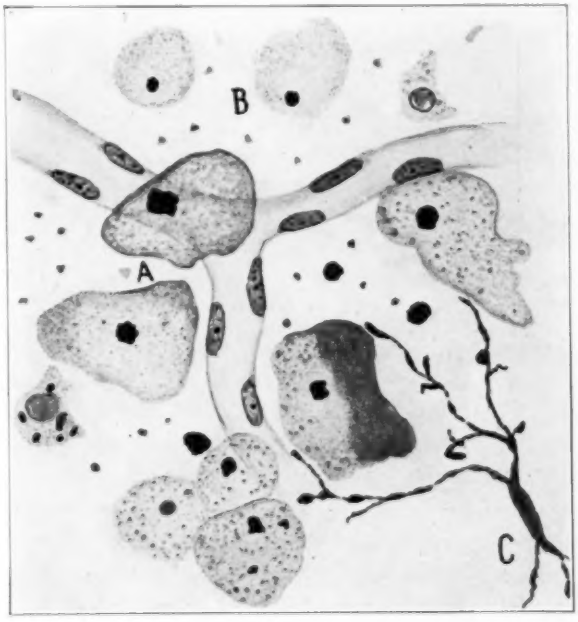

Fig. 5.—A group of ameboid cells gathered around a vessel. Note the difference in forms *A* and *B*. At *C* is a microgliocyte; silver carbonate stain of del Rio-Hortega.

round or elliptical forms (fig. 3*G*). In the final stage the nuclei are smaller than normal, deeply pyknotic and irregular in outline. Often in the pre-ameboid stage the processes are flexuous and wiry, probably an end-stage in their death, just before their disappearance from the cell body. Cells with such processes are seen in figure 3*F*. The relation of the ameboid cell to the vessels is striking though not surprising in view of the normal relationship of the fibrous neuroglia to the vessels. The vascular feet of the fibrous astrocytes are seen in process of disintegration (fig. 7). They are first margedly swollen to three or four times

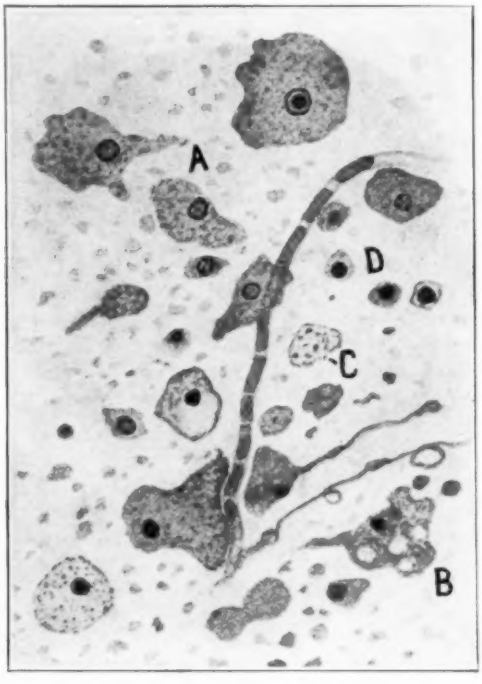

Fig. 6.—A group of ameboid cells around a vessel; silver carbonate stain of del Rio-Hortega.

their normal size (fig. 7*D*), vacuolated (fig. 7*C*) and coarsely granular, then tend to become finely granular or pulverized, and markedly shrunken (fig. 7*B*). In figure 7*B* is shown a group of vascular feet attached to a vessel, showing the swollen, vacuolated, coarsely granular forms, and finally the shrunken finely granular feet.

Of particular interest is the relation of the ameboid cells to the vessels. As has been pointed out, the greatest injury to the cerebral tissue was in the fibrous astrocytes and perivascular neuroglia of the white matter, and to a less extent of the gray matter. These cells, with their rich vascular connections and attachments, were the first to suffer

injury, and it is precisely these cells that are found in the production of ameboid cells, chiefly around vessels. In figures 4, 5 and 6 can be seen ameboid cells grouped around a vessel. Most of them are still attached to the vessel, but some are free in the tissue. In figure 4 at *B*, *C* and *E*, pre-ameboid forms are visible, while in figures 5 and 6 the cells are already ameboid cells.

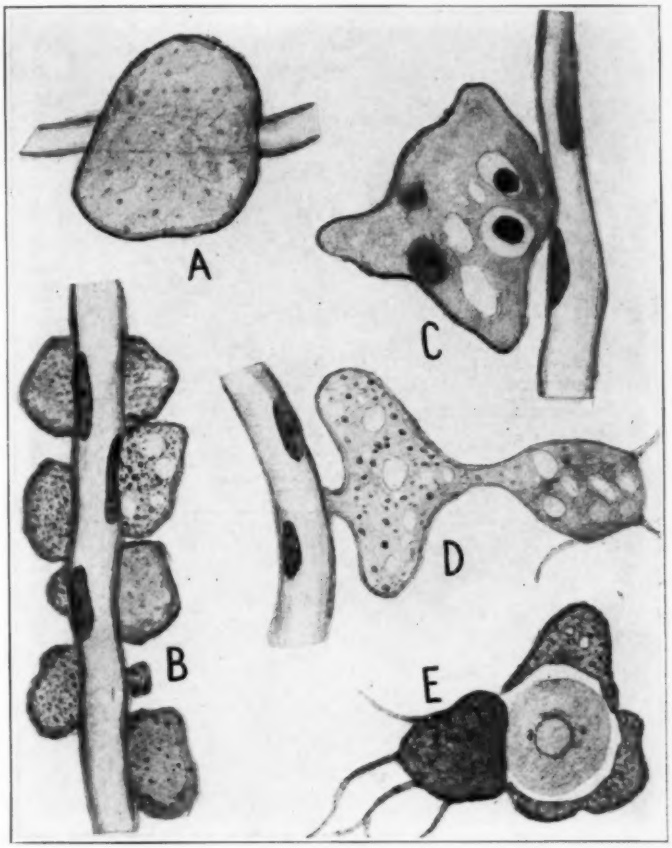

Fig. 7.—Changes in the vascular feet of astrocytic neuroglia. At *B* is a group of swollen, vacuolated sucker feet with two which are atrophic. At *C* is a markedly swollen and vacuolated sucker foot. At *D* is another swollen vascular foot and process; silver carbonate stain of del Rio-Hortega.

The perivascular neuroglia cells of Andriezen were also markedly diseased in the severe cases of intoxication. In the milder cases, they showed no change. The type of disintegration in these cells is seen in figures 8 and 9. Some are dark, pyknotic and fibrous. The common change is a nucleus retracted and homogeneous, with some cell processes

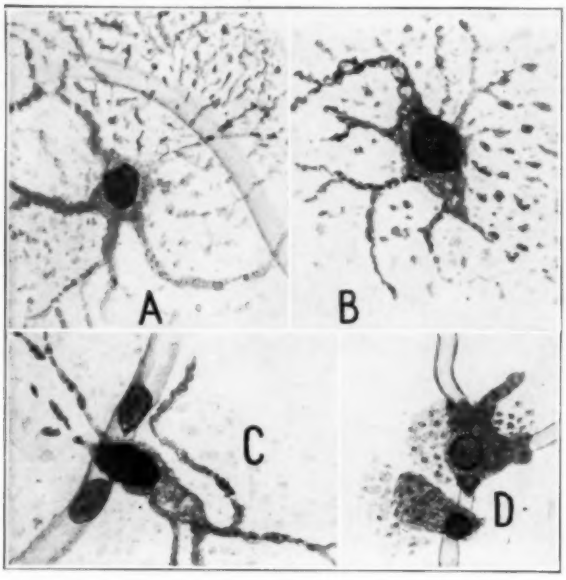

Fig. 8.—Degeneration of the perivascular neuroglia of Andriezen, showing granulation, fragmentation and hypertrophy of the prolongations; silver carbonate stain of del Rio-Hortega.

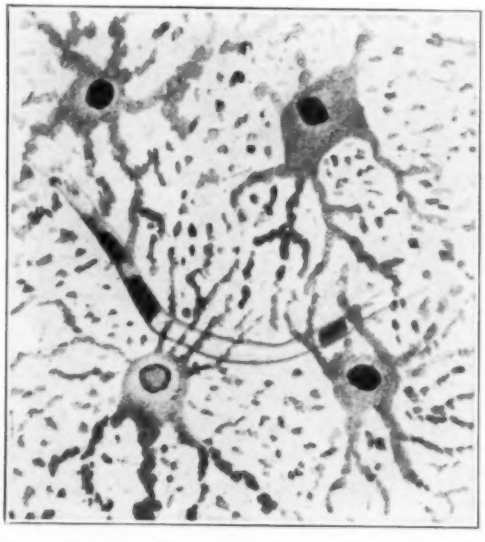

Fig. 9.—Degeneration of the perivascular neuroglia of Andriezen. At *A* there is granulation of the processes; at *B* is loss of processes and pyknosis of the nucleus. This is further advanced at *C*. At *D* the cell processes have been entirely lost; silver carbonate stain of del Rio-Hortega.

remaining and many apparently pulverized (figs. 8*A* and 9. Some cells exhibit complete destruction and appear as a mass of pulverized protoplasm embracing the vessel (fig. 8*D*). In figure 9 is seen a group of perivascular neuroglia with a definite loss of the rich arborization as it spreads across the vessel and with a hypertrophy and fragmentation of other processes. In figure 8*A* the processes are pulverized as they cross the vessel; in figure 8*B* there has been a marked loss of processes, a vacuolization of the cytoplasm and a pyknosis of the nucleus. This has progressed still further in figure 8*C*, so that only a few processes remain, and in figure 8*D* all that is seen of the perivascular neuroglia cell with its rich arborizations is an irregular mass of coarsely granular cytoplasm with a pyknotic nucleus. Some cells have been more injured than others; some contain more intact processes, and others are more pulverized, but all the perivascular neuroglia cells are diseased. This is true of those in the white cerebral substance, whereas the perivascular neuroglia cells in the gray matter are better preserved, though definitely injured.

Oligodendroglia.—These cells remained on the whole impervious to intoxication, except in the severe case of toxicity. Here marked changes were found, resulting in a complete disintegration of the cell. The process has been well described by Penfield and Cone. It is initiated with a slight swelling and vacuolization of the nucleus, which contains numerous small vacuoles and is hyperchromatic. The cytoplasm is swollen simultaneously and has a reticulated appearance. Then the nucleus becomes dark, with a well defined edge and a homogeneous structure (fig. 10 *P, T, V, W*). This is followed by a markedly pyknotic, shrunken nucleus and disintegration of the cytoplasm, which often remains as a few fine, granular wisps, appearing in the Nissl stain as an incomplete metachromatic bit of protoplasm (fig. 10 *A, B, C, D*).

Nerve Cells.—In contrast to the neuroglial elements, the nerve cells themselves were not markedly diseased by the uremic intoxication, though they showed evidences of pathologic changes. The only apparent change in the milder cases of toxicity was a more or less universal reduplication of the nucleolus (fig. 11). This was often doubled, and sometimes tripled and quadrupled in a single nucleus. Similar changes have been observed by Hortega in pilocarpine poisoning. In the case of severe intoxication, a similar change in the nucleolus was visible. The nuclei were often angular and somewhat shrunken (fig. 11) and the cytoplasm stained with a definite metachromatic tint. The latter was often vacuolated, and the Nissl bodies were occasionally disintegrated, though in most instances they were well preserved. The mildness of the changes in the nerve elements is in striking contrast to the widespread pathologic process in the various elements of the white matter, even in the severe uremic poisoning.

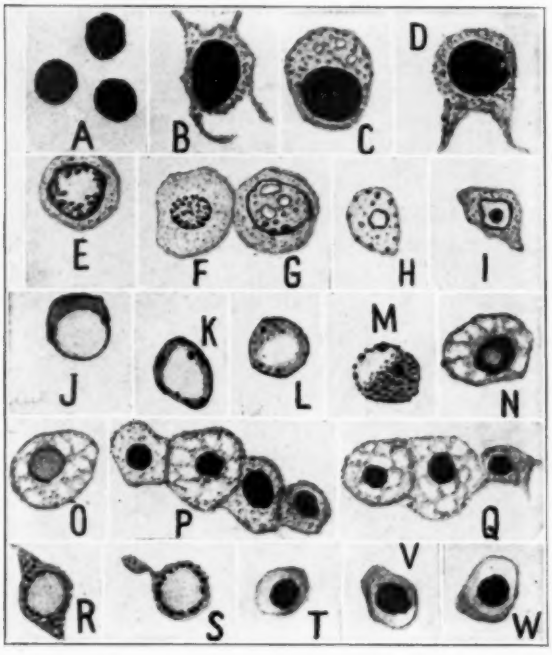

Fig. 10.—Degeneration of oligodendroglia; silver carbonate stain of del Rio-Hortega.

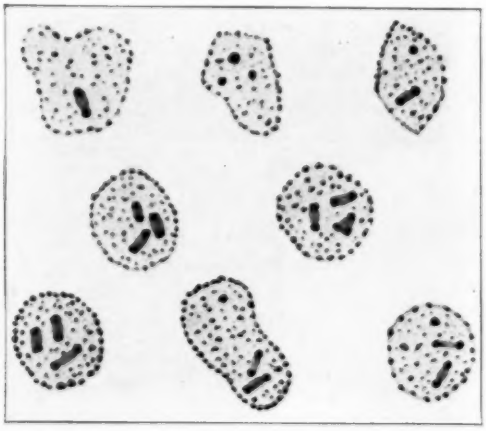

Fig. 11.—Reduplication of the nucleoli in nerve cells; Nissl stain.

Nerve Fibers.—Changes in the nerve fibers in the cerebrum, cerebellum, brain stem and spinal cord were not found, even in severe uremic poisoning. In all the cases, the axis cylinders remained completely intact.

COMMENT

Urea poisoning in the rabbit is attended by changes in the central nervous system, varying in intensity with the degree of toxicity. In the milder cases, produced by subcutaneous injection of urea, there is a slight hypertrophy of the fibrous astrocytes accompanied by milder changes in the nerve cells, evidenced by reduplication of the nucleoli. In the severe cases, produced by the intravenous injection of urea, there are marked pathologic changes in the fibrous astrocytes, with clasmatodendrosis and the formation of pre-ameboid and ameboid cells, destruction of the perivascular neuroglia of Andriezen, marked regressive changes in the oligodendroglia, moderately severe hypertrophy of the microglia with the production of nodosities and swellings, and relatively mild changes in the nerve elements themselves, shown by multiplication of the nucleoli and mild changes in the cytoplasm. It will be seen that in the severe cases the pathologic process involves much more severely the cerebral white matter and those elements of the gray matter in close relation to the vessels, notably the perivascular neuroglia and the protoplasmic astrocytes, the latter not so severely as the fibrous type, however. Even in the milder cases of uremic poisoning the changes noted involve first the elements with rich vascular attachments. This is a point of some importance, the significance of which will be dealt with later.

The microglia, taken as a whole in all the cases studied, reacted in a surprisingly passive manner. In the milder cases of intoxication, only an occasional cell showed what Hortega [1] describes as the earliest change in the microglia in pathologic processes, viz., an increase in the volume of the processes with a simultaneous shortening, resulting in hypertrophy of the cell. These hypertrophied microglia cells were few and probably of relatively little significance. In severe uremic poisoning the microglia gave evidence of a more advanced reaction, seen in the profuse production of nodosities and fusiform swellings along the processes, accompanied by hypertrophy of the latter with evidence of transition into rod cells. I have observed a similar change in the microglia in a case of Alzheimer's disease and in oligophrenia. Its significance is still obscure. Hortega [5] has described simple hypertrophy of the microglial protoplasm, produced by a retraction of the secondary and tertiary ramifications, in acute and subacute diseases of mild intensity as in uremia, general infections and meningitis. This is followed by a true hyper-

5. Del Rio-Hortega, P.: El tercer elemento de los centros nerviosos. Poder fagocitario y movilidad de la microglia, Bol. Soc. españ. de biol. **9**:154 (Nov.) 1919.

trophy in diseases of slow evolution as in dementia paralytica rabies and meningo-encephalitis. The simple hypertrophy of Hortega, however, is not the same as the hypertrophy with nodosities and fusiform swellings described in my case of severe uremic poisoning. Though this represents a change that has hitherto not been described, it is by no means specific, since it has been found not only in uremia, but in the other cases already mentioned. It probably represents a more advanced stage of microglial hypertrophy, due, as Hortega suggested, to a retraction of the processes and a condensation of the protoplasm.

Gitter cell or compound granular corpuscle formation did not take place in any of my cases. The absence of such cells is striking even in the severely injured brain of the case of profound uremic poisoning. This, therefore, is further proof, if such proof were necessary, of Hortega's [1] observation that the microglia forms compound granular corpuscles only in cases of frank cerebral destruction, as in wounds, hemorrhage and softenings, whatever may be the cause of the latter. Further evidence to this effect has been adduced by Mir,[6] who found a total lack of participation of the microglia in rabbits in cerebral compression which did not destroy the nerve tissue. In contrast to the failure of production of compound granular corpuscles, some evidence of the beginning formation of rod cells was observed in the transitional forms of microglia in my severe case of toxicity. No true rod cells were observed, though it is probable that if the poisoning had been permitted to go on long enough, such cells would have been observed in experimental urea poisoning, just as Hortega has found them in cases of uremia in the human brain. Transition forms between normal microglia and true rod cells were abundant however. The transitional rod cell forms already described probably represent a mild protest to the intoxication on the part of the microglia. Like the mature rod cells, they are mildly phagocytic in function, Achucarro [7] and later Hortega having demonstrated the presence of disintegrated products within their cell bodies. This phagocytic function, however, is mild, though universal, in deep experimental uremic poisoning. A more marked and more severe reaction on the part of the microglia would probably occur in severe cases of toxicity of long standing. Their mild reaction to uremic intoxication is further demonstration of the resistive power of microglia cells to toxic processes, in decided contrast to the ease with which such cells are mobilized in destructive processes within the brain.

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6. Mir, L.: The Reaction of the Neuroglia to Compression, to be published.

7. Achucarro, N.: Sur la formation de cellules à bâtonnet (Stäbchenzellen) et d'autres éléments similaires dans le système nerveux central, Trab. d. lab. de invest. biol. Univ. de Madrid **6**:82, 1908; Cellules allongées et Stäbchenzellen, cellules névrogliques et cellules granulo-adiposes à la corne d'Ammon du lapin, ibid. **7**:58, 1909.

A severe intoxication, which was able to produce all sorts of regressive changes in the neuroglia in my case, was able to produce only relatively mild evidences of hypertrophy in the microglia.

In contrast to the microglia, the fibrous astrocytes and perivascular neuroglia cells of Andriezen were more severely implicated.[8] Attention has been called to the fact that these changes were much more pronounced in the white matter than in the cortex, and that in the cortex those elements in close connection with the vessels, such as the perivascular neuroglia and the protoplasmic astrocytes, suffered most. The overwhelming involvement of the cells in close contact with the vessels is a matter of great importance. In white and gray substance it was elements such as the astrocytic and perivascular neuroglia which suffered most, though the entire brain was subjected to the same type of noxious injury. The degree of injury was greater in the white substance, but the involvement of the astrocytes and perivascular neuroglia in the cortex was clear. The fibrous astrocytes exhibited clasmatodendrosis and the formation of ameboid cells, while the perivascular neuroglia showed severe changes even to complete disintegration. The formation of ameboid cells has been well studied by Hortega,[3] and later by Penfield and Cone.[9] Their occurrence in toxic

8. Particular mention should be made of these special perivascular neuroglia cells. Andriezen (1893) described neuroglia cells forming a sort of adventitia around the vessels with their rich expansions. They represented to him a variety of fibrous astrocyte of mesodermic origin because of their contact with the vessels. Cajal stained these perivascular cells by the Golgi method and gave accurate illustrations of them, without, however, describing them. Hortega (Algunas observaciones acerca de la neuroglia perivascular, Bol. Soc. Esp. de Hist. Nat., April, 1925) was able to stain these cells clearly with his silver carbonate method, and was the first to make clear their morphologic characteristics. They possess many expansions profusely ramifying, unequaled in this respect by the protoplasmic cells of Cajal. The protoplasm is fine and in incomplete stains appears pulverized. The cells are more or less laminar, at times wide and bulky, extending semicircularly on a horizontal axis and rectilinearly on a longitudinal axis. They are situated on the vessel to which they adhere closely, and send their rich delicate expansions away from them. These expansions are short, terminating at a short distance from the vessel, or long and fibrillar, ending at a great distance from the vessel. They contain specific granules and pigments, and show a preference for the larger vessels. Their function is obscure, though it is possible, as Hortega has suggested, that by their close proximity to the vessels, they extract nutrition from these and disseminate it to the other nerve structures. To these special cells Hortega has given the name of "perivascular neuroglia of Andriezen" to distinguish them from the protoplasmic and fibrous astrocytes of Cajal.

9. Penfield, W., and Cone, W.: The Acute Regressive Changes of Neuroglia (Ameboid Glia and Acute Swelling of Oligodendroglia), Jahrb. f. Psychol. u. Neurol. **34**:204, 1926.

conditions is known (Jakob [10]). The history of beliefs concerning the nature of the ameboid cells has been well and clearly traced by Penfield and Cone,[9] who demonstrated that the change occurs both ante mortem and post mortem and is regressive in nature. Alzheimer [11] described ameboid cells in vivo. Cajal [12] later demonstrated their presence as a result of postmortem autolytic changes in the neuroglia cells, while Buscaino [13] produced ameboid cells in vitro by immersing normal tissues in acid or alkaline solutions of various concentrations. Alzheimer's belief that these cells represented bodies actively engaged in the removal of products of disintegration has not been substantiated in recent times. Hortega [3] demonstrated clearly that these cells represent regressive forms, and that they are not engaged in the process of phagocytosis. He accepted their presence both in vivo and post mortem, demonstrating the presence of altered gliofibrils in the form of whirls and rings in the former and their absence in the latter. Finally, Penfield and Cone [9] demonstrated the degenerative nature of these cells, pointed out their completely passive rôle in destructive processes in the brain, attributed to them no phagocytic power, and stated their belief in the presence of these cells locally before death and as a generalized manifestation as an agonal or postmortem change. Clinically, the ameboid cells are most effectively called forth in overwhelming intoxications (Hortega [3]), in edematous states of the brain (Wohlwill [14]) and in chronic conditions with acute excerbations (epilepsy, catatonia, rabies, meningitis, numerous toxic-infectious states and uremia). These facts are well known. It is not to these that I wish to direct attention, but rather to the fact that it is almost entirely in the white matter of the brain and in the neuroglia cells closely related to the vessels that the severest injury of these elements occurs.

A SUGGESTION CONCERNING THE FUNCTION OF NEUROGLIA

For a long time it has been known that the neuroglia contains specific granules. This phenomenon apparently was first observed in 1910 by Nageotte,[15] who found specific granules chiefly in the vascular

10. Jakob, A.: Anatomie und Histologie des Nervensystem, Leipzig, Franz Deuticke, 1927, vol. 1.

11. Alzheimer, A.: Beiträge zur Kenntnis der pathologischen Neuroglie und ihrer Beziehungen zu den Abbauvorgängen in Nervengewebe, Histol. u. Histopath. Arb. Nissl-Alzheimer **3**:401, 1910.

12. Ramón y Cajal, S.: Contribution al conocimiento de la neuroglia del cerebro humano, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:255, 1914.

13. Buscaino, V.: Sulla genesi e sul significato delle cellule ameboide, Riv. di patol. nerv. **18**:360, 1913.

14. Wohlwill, F.: Ueber ameboide Glia, Virchows Arch. f. path. Anat. **216**: 468, 1914.

15. Nageotte: Phénomènes de sécretion dans le protoplasme des cellules névrogliques de la substance grise, Compt. rend. Soc. de biol. **68**:168, 1910.

attachments of the neuroglia. From these observations he concluded that the neuroglia consisted of an interstitial gland annexed to the nervous system. Later in the same year, Mawas,[16] on the basis of his studies, reached similar conclusions. He observed that the ependymal cells and neuroglia contained variations in their chromatin similar to secretory cells, and that the cells and prolongations thereof contained mitochondria granules and lipoids. In 1913, Fieandt[17] observed granules within the glia recticulum of the gray matter and called these granules gliosomes. In the same year, Achucarro[18] stated the belief that the neuroglia neutralized the products of endogenous nerve metabolism and gave off an internal secretion which was ejected into the vessels and contributed to the total clinical harmony of the organism. This secretion, he believed, was responsible for vasodilatation and constriction in the cerebral vessels. Further than this, he believed that certain changes in the thyroid and testis, frequently seen in mental diseases, might be secondary to neuroglial lesions; moreover, according to Achucarro, the functional illnesses without apparent lesions may be explained by disturbances in the neuroglial secretion. Seen in this light, the neuroglia is a part of the endocrine system with an active chemical secretion. In 1914, Cajal[12] demonstrated the presence of gliosomes within the protoplasmic neuroglia, but failed to commit himself as to their significance. In 1925, Hortega[19] added to the knowledge concerning the specific granules in the neuroglia by demonstrating their presence in the oligodendroglia and, by showing a difference in the staining reaction of the gliosomes, mitochondria and the condriomas, indicated that the specific granules or gliaosomes were of a special chemical type. He, too, subscribed to the concept of the neuroglia as a secretory gland.

Overwhelming disease of the fibrous astrocytes and perivascular neuroglia cells in close association with vessels, in my case of severe urea poisoning, suggests a correlation of this injury with the specific

16. Mawas: Note sur la structure et la signification glandulaire probable des cellules névrogliques du système nerveux central des vertébres, Compt. rend. Soc. de biol. **69**:45, 1910.

17. Fieandt: Eine neue Methode zur Darstellung des Gliagewebes nebst Beiträgen zur Kenntnis des Baues und der Anordnung der Neuroglia des Hundhirns, Arch. f. mikr. Anat., 1910, vol. 76; Weitere Beiträge zur Frage nach der feineren Struktur des Gliagewebes, Beitr. z. path. Anat. u. z. allg. Path. **41**:247, 1911.

18. Achucarro, N.: Notas sobre la estructura y funciones de la neuroglia y en particular de la neuroglia de la corteza cerebral humana, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:273, 1914.

19. Del Rio-Hortega, P.: Condrioma y granulaciones especificas de las celulas neuroglicas, Bol. r. Soc. españ. de hist. nat. (Jan.) 1925, vol. 35, p. 1; Tercera aportacion al conocimiento morfologico e interpretacion funcional de la oligodendroglia, Mem. r. Soc. españ. de hist. nat. **14**:1, 1928.

functions of the neuroglia. Hortega has pointed out that, in addition to the secretory function of the neuroglia, there is probably also a nutritive function, especially in the case of the perivascular neuroglia cells of Andriezen. A third function seems also likely in view of the observations in my case, viz., a neutralization of toxic products circulating in the blood stream so as to prevent these noxious agents from reaching more vital parts of the nervous system.

The widespread injury of the neuroglia cells in close relation to the cerebral vasculature in my case of severe uremic poisoning suggests that this may be true. The markedly swollen and disintegrated vascular neuroglia cells of Andriezen and the almost equally severe injury of the fibrous astrocytes support this view. The more severe injury of the neuroglial elements in the white matter is not surprising in view of the fact that these elements have richer vascular attachments in this region than in the cortex. The perivascular neuroglia cells of Andriezen, which are numerous in the cortex, were hard hit in this region. In severe uremic poisoning, therefore, I found a profound injury of all the neuroglia cells in close relation to the cerebral vasculature, with more marked involvement in the white matter than in the cortex. This has suggested the possibility that the neuroglia possesses a function, the object of which is to neutralize the effect of noxious agents circulating in the nervous system, and in this way to protect the nobler elements against harm. So long as the amount of toxin is small, the neuroglia can cope with it. As soon as it becomes overwhelmingly great, the excess which cannot be cared for spills over into the nerve tissue and attacks these elements.

CHANGES OF THE SPINAL CORD IN HODGKIN'S DISEASE

REPORT OF TWO CASES, WITH AN UNUSUAL SKIN MANIFESTATION IN ONE *

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Hodgkin's disease is noted for its ubiquitous appearances. Wherever lymphatic tissue exists in the body, lymphogranulomatosis may occur. Wherever it appears, it initiates a series of local, and distant, secondary changes. These, partly specific and partly nonspecific, account for a wide variety of clinical syndromes which follow. The variability of the disease is a byword. It assumes all forms and shapes. Several of the more unusual, clinical and pathologic vagaries of Hodgkin's disease were combined in the following cases.

REPORT OF CASES

CASE 1.—*Clinical History.*—A colored woman, aged 32, entered the Cook County Hospital insisting that she had always been well until three weeks before. Casually she mentioned that one year before, while in another city, she had had a gradual swelling of the glands of the neck, one of which had been removed for biopsy; a diagnosis of Hodgkin's disease had been made. She had been given an intense course of roentgen therapy, and the swelling of the glands had subsided.

She had lost a little weight, but had been feeling well until three weeks before admission, when she first noticed numbness and tingling in both feet. The day after, she found that she could hardly move the right leg. The following day, she lost the use of the left leg. She went to bed and found then that she could no longer control urination or defecation. She had a slight cough, which seemed somewhat brassy, and a little pain in the left side of the chest.

Physical Examination.—The patient was rather well nourished on entrance but appeared acutely ill, with a temperature of 100.4 F., a pulse rate of 120 and respirations of 40 per minute. The heart appeared normal. The liver was enlarged, its inferior edge being three fingerbreadths below the costal margin. The spleen was not palpable.

Many firm, discrete lymph nodes were palpable on both sides of the neck. A collection of similarly enlarged and firm nodes were felt in the left axilla. On the left side of the neck, just below the ear, was a large ulcerated mass, 5 by 7 cm. in diameter.

There was some impairment of resonance over both lung fields and a few moist râles, but no other signs. Roentgen examination showed a great increase in the width of the shadow of the superior mediastinum and right hilus. The

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density diminished diffusely toward the periphery of the lung on the right, and extended down to a sharply demarcated line at the level of the third rib.

Many firm nodules of the size of a pea were distributed irregularly throughout the skin over the anterior wall of the chest, especially over the left mammary gland. There were also a large, sloughing decubitus ulcer, 15 cm. in diameter, over the sacrum and smaller ulcers over the opposing medial condyles of the femurs.

Neurologic Examination.—All power of motion had disappeared from both lower extremities. Both legs were limp and flaccid, with all reflexes absent. The rectal sphincter was relaxed. Sensation to pain, temperature, touch, pressure and position was diminished below the fourth thoracic segment and altogether lost below the level of the eighth thoracic segment.

The cranial nerves were normal. Motion, coordination and sensation were likewise intact in the upper extremities, and above the fourth thoracic dermatome. Roentgenograms of the spine disclosed no vertebral pathologic changes.

Laboratory Examinations.—The Wassermann reactions of the blood and cerebrospinal fluid were negative. The red blood cell count was 4,300,000, the leukocyte count 8,000 per cubic millimeter.

Clinical Diagnosis.—The clinical diagnosis was Hodgkin's disease involving the lung and skin, with transverse myelitis at the fourth thoracic segment, arising from involvement of the vertebra or from granulomatous masses in the canal.

Course.—The huge, sloughing, trophic ulcers prohibited further diagnostic manipulations. The patient had a septic temperature of from 103 to 105 F. She died in a state of severe toxemia from the extensive, infected ulcerations, ten days after entrance to the hospital, just one month after the onset of serious symptoms.

Necropsy.—Macroscopic Examination: By the time of death, the body had become emaciated, the eyeballs sunken, the conjunctivae and oral mucosa pale. The sacral region was excavated by an ulcer, 16 cm. in diameter, extending to a depth of 5 cm. into the gluteal tissues on either side. The floor and edges were covered by a green, foul, purulent and necrotic tissue. The sacrum and coccyx were exposed and eroded. Small, superficial, crusted decubitus ulcers were present also over the opposing medial condyles of the femurs and over the heels.

In the left, posterior cervical triangle was a superficial, irregular, oval ulcer, 4 cm. in diameter, with an indurated margin, a sloping edge, a clean, yellowish-red floor and a firmly indurated base. At the lower border of the ulcer were several nodules, from 8 to 15 mm. in diameter, elevated from 2 to 3 mm. above the surface. They were attached to the skin and rendered it thin and glossy. A few similar nodules were scattered over the skin of the chest, especially in the upper lateral quadrant of the left breast.

Most of the upper lobe of the right lung was replaced by a firm, lobulated, pinkish-gray mass which started from the hilus and surrounded the branches of the bronchus. Grossly, the condition looked like a bronchogenic carcinoma. The left upper lobe was similarly, but less extensively, involved. The intervening mediastinum was infiltrated by firm, white tissue.

At the hilus of both lungs, at the bifurcation of the trachea and in the axilla the lymph nodes were enlarged up to 2.5 cm. in diameter. They were discrete and firm, and of a light pinkish-gray mottled with grayish-white areas. On the left side of the neck the nodes were matted together to form a dense, gray mass from 2 to 3 cm. thick.

The spleen weighed 165 Gm. Its pulp was soft and contained no nodules.

The liver weighed 2,000 Gm. It contained no tumor nodules.

The combined weight of the kidneys was 335 Gm. On the posterior aspect of the left kidney were two whitish nodules 2 mm. in diameter.

In the epidural space, at the level of the third and fourth thoracic vertebrae, the posterior aspect of the dura mater of the spinal cord was covered by a firm, yellowish-gray, plaquelike thickening, 30 mm. long, 15 mm. wide and from 2 to 4 mm. thick. There was no pressure groove on the underlying cord.

Microscopic Examination: The plaque described over the dura mater spinalis was composed of a cellular and fibrillar tissue. It had infiltrated fully the external half of the dura mater, isolated fibrous bundles of which were scattered through the plaque. It was sharply limited, however, by the intact internal half of the dura mater. Embedded in the loose network of the plaque was a great variety of cells. There were many multilobulated giant cells with oxyphilic nucleoli, histiocytes, lymphocytes and fibrocytes in great confusion. The greatest cellularity was found in the center. Toward the periphery the tissue became more and more fibrotic.

On the internal surface of the dura mater there was no granulomatous tissue, but an altogether different type of reaction was found. There was a diffuse, marked infiltration by numerous polymorphonuclear leukocytes and by a smaller number of lymphocytes.

At the level of the plaque, the large bundles of the spinal nerve roots, especially the posterior, were surrounded, at the reflection of the dura mater over them, by dense, cellular accumulations (fig. 1). These were composed of a few leukocytes scattered between more numerous, prominently large cells. The latter were two or three times the size of a lymphocyte. They were round or oval, with a narrow rim of cytoplasm. A few were branched or elongated. Their nuclei were large and rich in a reticular chromatin. An occasional mitotic figure was found (fig. 2). These accumulations filled the subdural and subarachnoid spaces at the angles where the dura mater and arachnoid were reflected over the nerve roots. They lay between the root bundles but did not invade them. Above and below the level of the plaque these cells, as well as the leukocytes, were present in only small number, and no obliteration of the perineural spaces was seen.

Corresponding to the level of the accumulations, the structure of the spinal cord and of the arachnoid and intraspinal portions of the nerve roots were much changed. The white matter especially had lost its normal appearance. There was a marked vacuolation and disintegration of the nerve fibers and their myelin sheaths. The entire white matter appeared areolar and rarefied, a sieve of "Luecken" and fat droplets with the sudan III stain. There was proliferation of the glia cells, which appeared as gitter cells filled by lipoid droplets. These changes were distributed widely through the nerve roots and anterior, posterior and lateral columns of the cord. The ganglion cells of the anterior horns showed severe regressive changes. Only a few cells had retained their nuclei.

Above and below this level, the changes in the cord were slight. In the lumbar cord, the descending tracts showed slight degeneration and a few lipoid droplets with Weigert and sudan III stains. In the cervical region, the ascending tracts were similarly but slightly involved.

The epidermis over the skin nodules was thin and the papillae were flattened. The cutis contained dense, cellular filtrations which were arranged about the blood vessels and sweat glands. They extended even into the subcutaneous fat tissue.

They were made up of lymphocytes, large histiocytes and the characteristic multilobulated giant cells.

In addition to the infiltrations, there were groups and strands of large, pale-staining cells. These were sharply differentiated from the remaining dense connective tissue of the cutis, and prominent against the adjacent polymorphocellular infiltrations. Under a high power lens, the groups were found to be composed

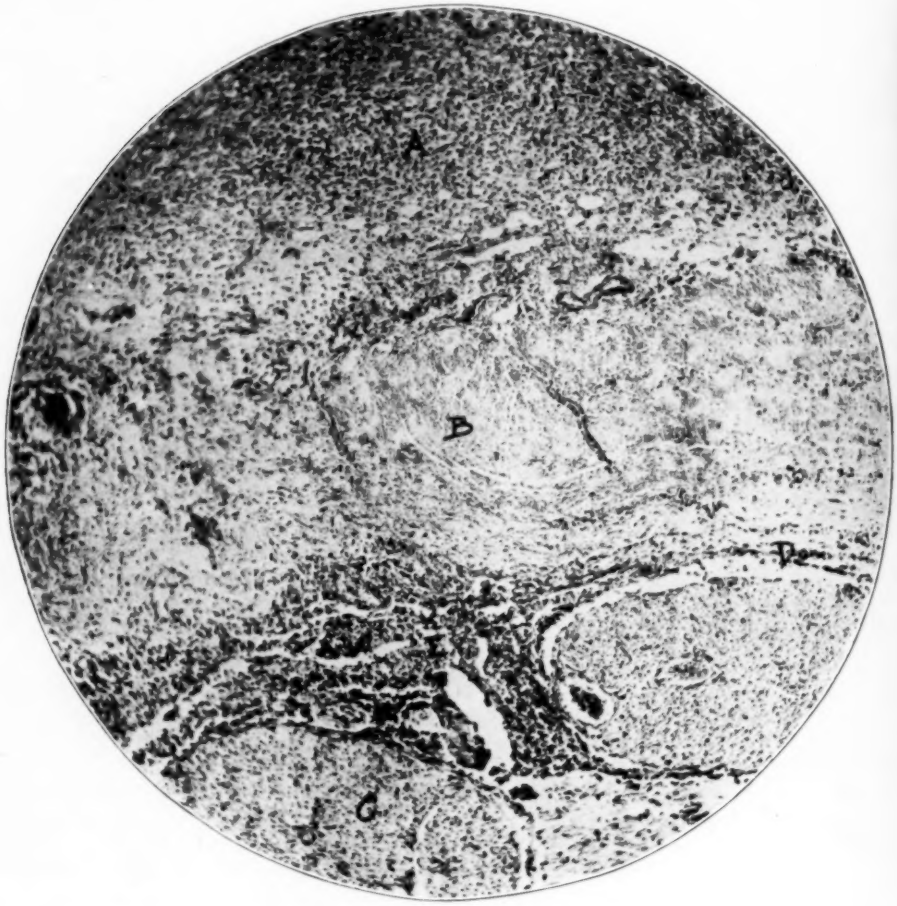

Fig. 1.—Angle of reflection of the dura over the spinal nerve roots. *A*, lymphogranulomatous infiltration of the external layers of the dura, limited by the intact *B*, internal layers of the dura; *C*, spinal nerve roots; *D*, diffuse infiltration with polymorphonuclear leukocytes; *E*, accumulations of arachnoid cells in the subdural and subarachnoid spaces, at the angles of reflection of the meninges over the nerve roots. Leitz apochromatic; 16 mm.; microplanar 2.

of large, vacuolated, light stained cells; their abundant, delicate cytoplasm surrounded small, oval, light-stained nuclei (fig. 3).

The whitish nodules in the left kidney were composed of polymorphocellular infiltrations, similar to those described.

No lymphogranulomatous nodules were found in the spleen even microscopically.

The firm areas in the upper lobes of the lungs, which grossly resembled the appearance of bronchogenic carcinoma, were seen microscopically to be composed of typical lymphogranulomatous tissue, with no evidence of malignancy. The lymph nodes were composed of similar tissue.

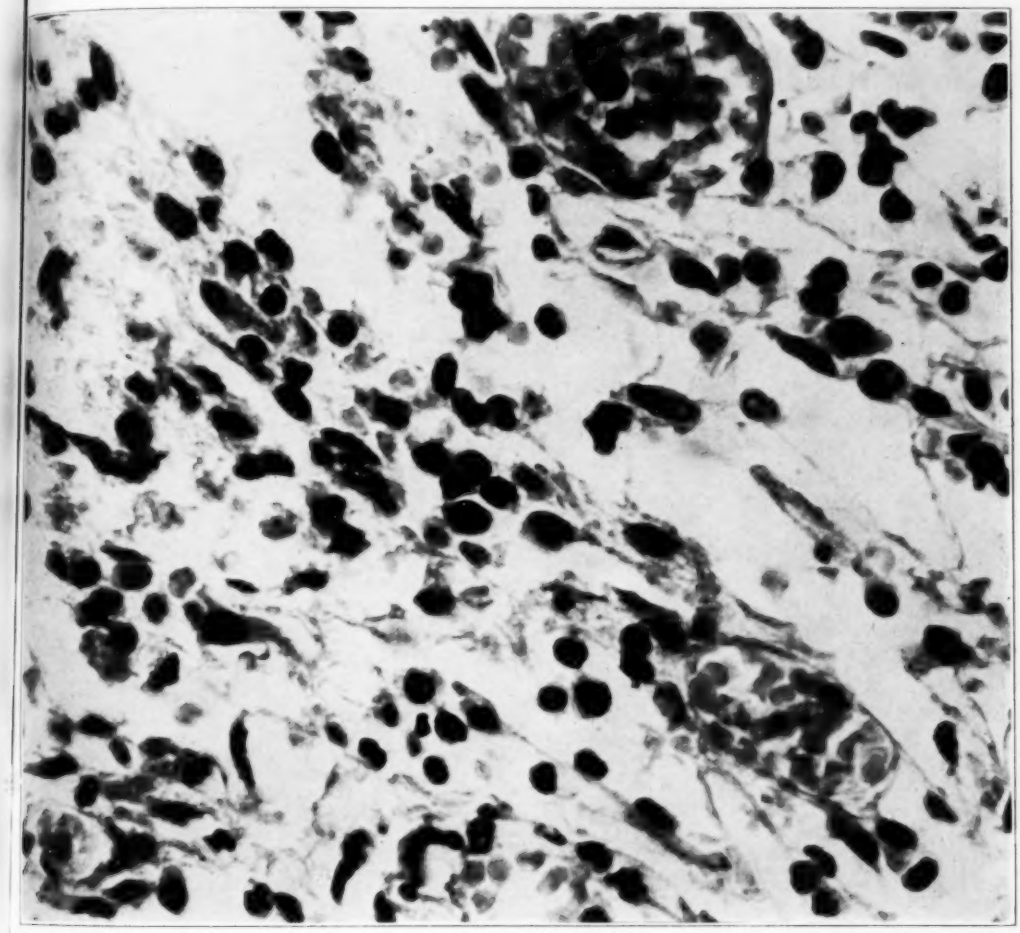

Fig. 2.—Accumulations of arachnoid cells in the duraneural angles. High power view to show cytoplasmic and nuclear detail. Leitz apochromatic; 4 mm.; microplanar 4.

Anatomic Diagnosis.—The diagnosis was: (1) lymphogranulomatosis of the dura mater spinalis at the level of the third and fourth thoracic vertebrae; (2) focal degenerative myelomalacia of the cord at this level, with early ascending and descending degeneration; (3) lymphogranulomatosis cutis; (4) lymphogranulomatosis of the lungs; (5) lymphogranulomatosis of the left cervical, axillary, subpectoral, mediastinal, tracheobronchial and pulmonary lymph nodes; (6) gran-

ulomatous nodules in the left kidney; (7) granulomatous infiltration of the subpleural lymph vessels of the thoracic wall; (8) subacute tumor of the spleen, without granulomatous involvement; (9) extensive decubitus ulcer in the sacral region, exposing the sacral bone and excavating the gluteal tissues, and (10) parenchymatous degeneration of the myocardium, liver and kidneys.

Case 2.—*Clinical History.*—A colored woman, aged 30, had complained of ill health for a period of seventeen months. The trouble began with a "bad cold

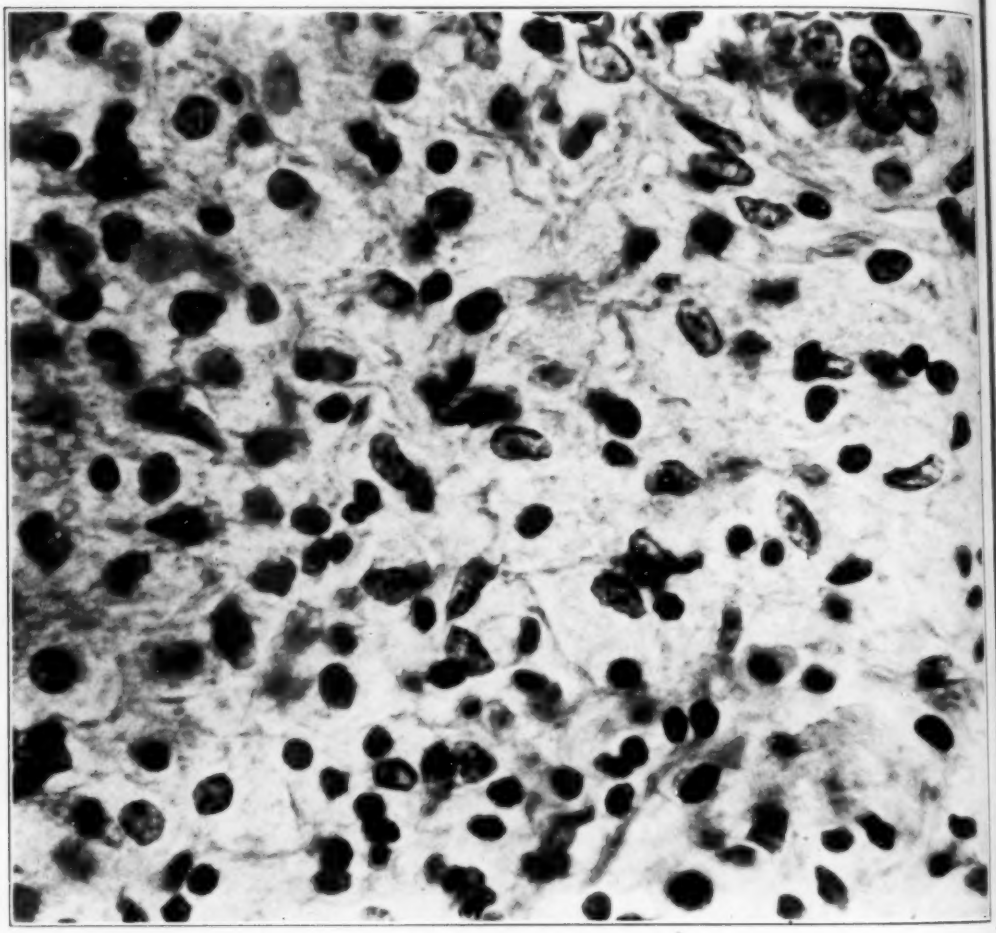

Fig. 3.—Pseudoxanthomatous cells which were found between the lymphogranulomatous cords of the cutaneous nodules. Same magnification as in figure 2.

which hung on," with persistent cough and progressive dyspnea. In November, 1928, she entered the Cook County Hospital for the first time. A diagnosis of Hodgkin's disease was made. She was given a course of roentgen therapy, and was discharged in March, 1929, as improved.

She returned in April, 1929, complaining again of dyspnea and cough. The dyspnea was inspiratory and the cough brassy. There was flatness over the left

upper pulmonary lobe, and no breath sounds were audible there. A wide area of mediastinal dulness was percussed, which corresponded to the x-ray determination of a "ragged shadow at the hilum." A second course of roentgen treatments was given, which afforded considerable relief. A dull substernal pain persisted, however, and failure of health continued relentlessly. She lost weight steadily, falling from 105 to 75 pounds (47.6 to 34 Kg.) within six months.

She reentered the hospital in August, 1929, with new complaints of: (1) Paresthesias of various kinds in both lower extremities. From the waist line down to the toes, there were irregular and variable areas of numbness, tingling and sometimes of almost unbearable burning sensations. There were girdle sensations of "tightness about the stomach" which came on most often at night. (2). Weakness, particularly in the lower extremities. This had gradually increased, until, on admission, she was unable to walk or even to stand unsupported. (3). Inability to control urination or defecation, which had begun four days before entrance. She related also that two months before, she had had a single hemoptysis of from 3 to 4 ounces of bright red blood.

Physical Examination.—The patient was poorly nourished, dyspneic with wheezing respirations and coughed intermittently. Two peanut-sized, firm discrete lymph nodes were palpable, lying over the external jugular vein. Biopsy of one of them showed Hodgkin's lymphogranuloma. Over the left, upper pulmonary lobe there were flatness and absence of breath sounds. Both lower extremities were cold and clammy.

Neurologic Examination.—The cranial nerves were normal. Strength, reflexes and sensation in both upper extremities were fairly well preserved. The abdominal reflexes were absent. Both lower extremities were flaccid and almost powerless, without, however, any definite paralysis being demonstrable. The deep reflexes were weak but present; the Babinski sign was variable. Below the level of the xiphoid, pain, touch and temperature sensation were here and there impaired, with irregular areas of hyperesthesia and paresthesia of all kinds. At repeated examinations, all these neurologic signs were confusingly and widely variable. The only constant and marked observation was a complete loss of sense of position in both lower extremities. A roentgenogram of the spine showed no pathologic changes of the bone.

Laboratory Examinations.—The Wassermann reactions of the blood and spinal fluid were negative. The hemoglobin was 70 per cent, the red blood cells numbered 3,740,000 and the leukocytes 8,200, with no abnormal forms.

Clinical Diagnosis.—The clinical diagnosis was substernal and abdominal Hodgkin's disease with involvement of the spinal cord.

Course.—Roentgen therapy was again instituted. In the middle of August, a decubitus ulcer appeared over the sacrum. The left leg became slightly edematous, and the patient began to have an irregular temperature. Early in September, another decubitus ulcer developed over the right trochanter. The left leg became enormously swollen, and the patient began to show a definitely septic fever. The trophic changes progressed steadily, in spite of sedulous nursing care, until at the time she died, two and one-half months after entrance, there was a huge sacral ulcer widely excavating both gluteal regions.

Necropsy.—Macroscopic Examination: The body was emaciated, the eyeballs were sunken and the lips and oral mucosa were pale. None of the superficial lymph nodes were palpable. The extensive sacral decubitus ulcer exposed the bone; its floor was covered by foul, dirty yellowish-gray, necrotic and purulent

material. There were similar smaller ulcers on the inside of the left knee and over the external condyle of the right tibia.

At the bifurcation of the trachea, on the inferior aspect, was an irregular opening, 3 mm. in diameter, with soft, dirty grayish-green edges. The opening was partly occluded by grayish purulent material. On the median aspect of the main bronchus to the right lower lobe, an ulcer, 5 mm. in diameter, exposed one of the cartilaginous rings. On the posterior aspect of the same bronchus, adjacent to the ulcer, was an irregular cavity, 45 by 20 mm. in diameter, lined by soft light yellowish-gray tissue, filled by foul, grayish-green pus. There was a

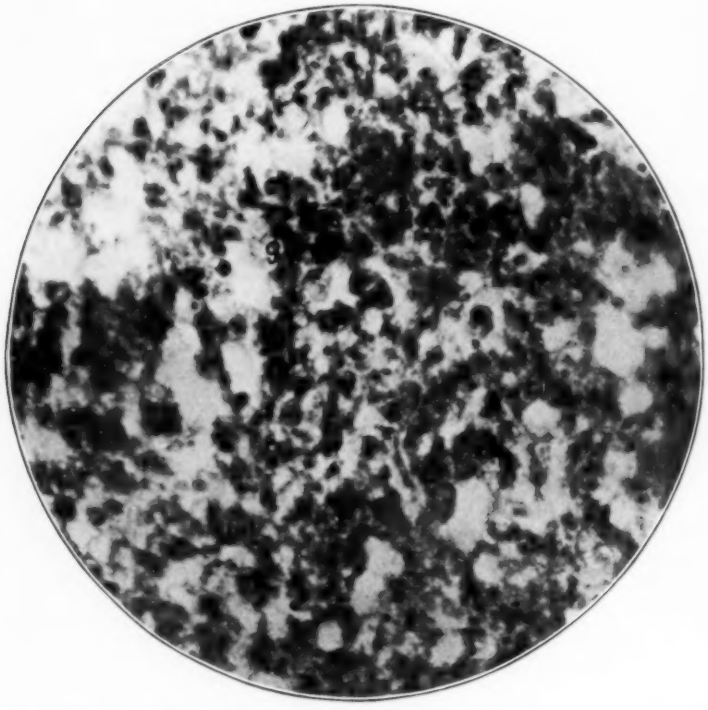

Fig. 4.—High power view of degenerative changes in the posterior columns of the spinal cord in case 2. Note the rarefaction and the gitter cells filled with lipoid droplets (*g*); × 180.

similar cavity, 25 by 20 mm. in diameter, between the left main bronchus and a group of enlarged lymph nodes.

The lymph nodes at the bifurcation of the trachea and along its right side were firm, enlarged up to 30 mm. in diameter, anthracotic and mottled with light yellowish-gray areas. One of them was stony hard and brittle. At the hilus of the left lung, they were firm, yellowish-gray and enlarged up to 10 mm. in diameter. The lower lobes of both lungs were purplish red, moist with foamy fluid and showed irregular confluent, granular areas of consolidation.

The periaortic abdominal lymph nodes were soft, light purpuish gray and enlarged up to 15 mm. in diameter. The peripancreatic nodes were firm and enlarged up to 25 mm. in diameter.

The spleen weighed 140 Gm.; it was moderately firm and showed no nodules. No macroscopic changes were present in the spinal cord.

Microscopic Examination: The spinal cord showed marked changes throughout. At the midthoracic level, the changes severely affected the entire posterior column. In the lateral columns, the peripheral zone, including the dorsal and ventral spinocerebellar and lateral spinothalamic tracts, and the dorsolateral fasciculus were almost as severely involved. The intermediate zone (pyramidal and rubrospinal tracts) were only moderately affected, the central zone of propria fibers even less. The anterior columns were intact. Other levels of the cord showed practically the same changes.

With the sudan III stain, the involved areas were seen to be riddled with numerous "Luecken." They showed marked degeneration of the nerve fibers and myelin sheaths, with numerous free lipoid droplets and "gitter" cells (fig. 4). There were also fat-containing cells in the adventitial spaces of the adjacent blood vessels, in the septums accompanying them and in the leptomeninges of the cord.

In the pons varolii there was a single small accumulation of glia nuclei (oligodendroglia) and numerous small hemorrhages. The brain was otherwise normal.

Even microscopically, no specific nodules were seen in the spleen.

Except for a narrow marginal zone of lymphatic tissue, the lymph nodes were composed of dense sclerotic connective tissue. This was interrupted by islands of lymphocytes, fibrocytes, plasma cells, large lymphoid round cells and the typical multilobulated giant cells.

Anatomic Diagnosis.—The diagnosis was: (1) Hodgkin's granuloma of the peritracheal, left pulmonary and peripancreatic lymph nodes; (2) decubitus ulceration at the bifurcation of the trachea, and of the main bronchus to the right lower pulmonary lobe; (3) peritracheal abscess in the region of the bifurcation; (4) aspiration pneumonia in both lower pulmonary lobes; (5) subacute degeneration of the posterior and lateral columns of the spinal cord; (6) focal septic hemorrhages of the pons; (7) extensive decubitus ulcers; (8) diphtheritic cystitis and proctitis.

COMMENT

The nature of Hodgkin's disease is still in doubt (Simmonds [1]), but it is conceived of generally as an inflammatory disease of the reticulolymphatic tissues (Gibbons [2]) The specific organism, if one exists, has not as yet been identified with certainty. The subjects afflicted are presumably sensitized in such fashion that their reticulolymphatic apparatus and bone-marrow will react in a specific manner to it (Symmers [3]). On reinfection, they produce locally the characteristic polymorphocellular granulation tissue. This tissue invades adjacent vital structures by direct extension. It arouses nonspecific perifocal inflammatory reactions, produces secondary local mechanical

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2. Gibbons, H.: The Relation of Hodgkin's Disease to Lymphosarcoma, Am. J. M. Sc. **132**:692, 1906.

3. Symmers, D.: Certain Lesions of the Lymph Nodes, New York M. J. **93**:971, 1911; Clinical Significance of Pathological Changes in Hodgkin's Disease, Am. J. M. Sc. **167**:157 and 313, 1924.

damage and induces other nonspecific pathologic changes in both local and distant organs.

Involvement of Nervous System.—That the condition may involve the central nervous system, particularly the cord, has long been known. "Hodgkin's paraplegia" has been described many times; by Eichhorst in 1898,[4] by Walthard,[5] Urechia,[6] Carslaw,[7] East[8] and Forrest.[9] Von Hecker[10] and Askanazy[11] have reported cases with epileptiform attacks from granulomatous cerebral lesions in the centrum semiovale. Blakeslee[12] reported one unusual case of thirteen years' duration with recession of the spinal symptoms after roentgen therapy. Weber[13] reviewed the various immediate causes of the paraplegia found in these cases.

The spinal symptoms are nonspecific. They are a result of the damage to the spinal cord, no matter what its mechanism. They may appear by reason of the effects of local granulomatous lesions or of toxic damage from distant lesions. Of the first type, cases have been described of: (1) invasion of the epidural space through the intervertebral foramina, from lymphogranulomatosis arising in the lymphatic tissue of the fascia or muscles of the back (East and Lightwood); (2) invasion of the epidural space, from subperiosteal lesions in the vertebrae (Weber); (3) involvement of the bodies of the vertebrae: (*a*) with collapse of the vertebral bodies (Askanazy) and (*b*) without such collapse (Carslaw); (4) isolated granulomatous deposits in the epidural tissue and in the dura mater spinalis.

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4. Eichhorst, H.: Deutsches Arch. f. klin. Med. **61**:519, 1898.

5. Walthard, K.: Rueckenmarkweichung bei Lymphogranulom, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:1, 1925.

6. Urechia, C. I., and Goia, I.: Lymphogranulomatose de la moelle, Presse méd. **35**:179 (Feb. 9) 1927.

7. Carslaw, J., and Young, J. S.: Case of Hodgkin's Disease with Paraplegia, Glasgow M. J. **108**:193 (Oct.) 1927.

8. East, C. F. T., and Lightwood, R. C.: Compression Paraplegia in Lymphadenoma, Lancet **2**:807 (Oct. 15) 1927.

9. Forrest, D.: Transient Paraplegia in Hodgkin's Disease, Lancet **2**:809 (Oct. 15) 1927.

10. Von Hecker, H., and Fischer, W.: Zur Kenntnis der Lymphogranulomatose, Deutsche med. Wchnschr. **48**:482 and 520, 1922.

11. Askanazy, M.: Lymphogranuloma des Knochenmarks, Verhandl. d. deutsch. path. Gesellsch. **18**:78, 1921.

12. Blakeslee, G. A.: Compression of Spinal Cord in Hodgkin's Disease: Recession After Roentgen Therapy, Arch. Neurol. & Psychiat. **20**:130 (July) 1928.

13. Weber, F. P.: Paraplegia and Cauda Equina Symptoms in Hodgkin's Disease, Quart. J. Med. **17**:1, 1923-1924; Paraplegia in Lymphogranulomatosis and Leukemia, Internat. Clin. **1**:126, 1926.

Of the second type, cases have been described with no local lesions, but with the toxic changes in the spinal cord of: (1) subacute combined degeneration, (2) diffuse myelitis (Forrest) and (3) syringomyelia-like gliosis. In addition, one case of Hodgkin's disease was described with a paraplegia resulting from a tuberculous Pott's disease, from which the patient was simultaneously suffering (Weber).

Case 1 described in this paper is an example of paraplegia caused by isolated lymphogranulomatous growths involving the dura. The epidural tissues of the cord are filled by a fat-laden, reticulolymphatic tissue. The dura mater spinalis is not a uniform coat of fibrous tissue. It is divided into longitudinal layers by varying but normally slight amounts of loose reticular tissue. The Hodgkin's granulomas develop in the epidural and intradural tissues. The local sessile histiocytes swell up, proliferate and form giant cells. Cells are deposited from the blood stream. The typical polymorphocellular granulation tissue of Hodgkin's disease, with histiocytes, giant cells, lymphocytes and eosinophils, is produced.

It formed an epidural plaque, 2 mm. in diameter, over the posterior aspect of the dura mater. It splintered the dura mater, foci of granulation tissue separating widely its fibrous layers. It penetrated, but did not perforate, the dura, the internal half of which was still intact and still kept the lymphogranuloma on the outside. No Hodgkin's tissue was found on the inside of the dura or invading the cord.

It was evident that the epidural plaque had not produced the severe degeneration of the underlying cord by any direct compression. The plaque was not thick; there was some free space between the dura and the cord. The underlying cord showed no deformity, no sign at all of a pressure groove. How then did the tumor on the outside of the dura cause, without compression, degeneration of the cord within?

The same question has been asked in cases of paraplegias from other types of extradural tumor without compression, in Pott's paraplegia without vertebral collapse, in extradural abscesses, in tabes and in syphilitic meningitis. A common answer was found on examining the inside of the dura mater at the level of the lesion. The epidural and intradural granuloma had aroused a nonspecific reaction of the underlying pia-arachnoid membranes.

The vascular pia mater responded with a dilatation of its capillaries and an emigration of lymphocytes and of numerous polymorphonuclear leukocytes. These cells were evenly deposited in a thin layer under the arachnoid. Of undetermined significance, their presence is ascribed to a nonspecific, perifocal reaction. They have little to do with either the specific character of the Hodgkin's lesion or the degeneration of the cord.

The arachnoid is avascular, but its "mesothelial" cells are close relatives to the sessile histiocytes of other parts of the body. They are seen in small numbers normally. They are seen in large numbers in tabes, in extradural abscess and in many other lesions associated with degeneration of the cord. They precede, rather than follow, such degeneration (Stern [14]). They are called "granulation cells" by Richter [15] and "membrane cells" by Key and Retzius.[16] It is better perhaps to call them, as Hassin does, "arachnoid cells." [17] In response to any extradural irritation they proliferate. They proliferate so actively that mitotic figures can be seen among them.[17]

Masses of these cells form particularly in the angle where the arachnoid and dura reflect over the nerve roots. They are seen between the nerve bundles, especially of the posterior roots, and here cause the early paresthesias. Rarely are they seen to penetrate the nerve fascicles themselves. They do not, as Richter holds, induce degeneration of the cord by strangulating the nerves.

However, they obstruct and obliterate the subdural and subarachnoid spaces about the nerve bundles at the points of reflection described. These spaces, according to Key and Retzius,[16] are the principal avenues of escape of the spinal fluid from the subarachnoid space and of the tissue fluids of the cord itself. With the blocking of drainage, the tissue fluids are dammed back in the parenchyma of the spinal cord and destroy its fibers. Above and below the level of the lesion there develop no such arachnoid proliferations and no such destruction of the cord. There is seen only the slight ascending and descending tract degeneration which barely has had time to develop from the focal degenerative myelopathy at the level of the plaque. Thus, according to Hassin,[17] can cord damage appear without cord compression.

The same mechanism seen in this case of Hodgkin's paraplegia may be applied to the other conditions already mentioned. It differs only in time effect, in severity and extent of the lesion. In tabes it is slow, and long drawn out. In extradural abscess it is acute, severe and diffuse. These differences may be almost wholly responsible for the variations in the cord damage and in the consequent symptomatology of these conditions.

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15. Richter, H.: Zur Histogenese der Tabes, Ztschr. f. d. ges. Neurol. u. Psychiat. **67**:1, 1921.

16. Key, A., and Retzius, G.: Studien in der Anatomie des Nervensystems, Arch. f. mikr. Anat. **9**:308, 1873.

17. Hassin, George B.: Tabes Dorsalis, Pathology and Pathogenesis, Arch. Neurol. & Psychiat. **21**:311 (Feb.) 1929; Circumscribed Suppurative Peripachymeningitis, ibid. **20**:110 (July) 1928; Disseminated Sarcomatosis of the Central Nervous System and the Meninges, ibid. **21**:1087 (May) 1929.

Case 2 is an example of subacute combined degeneration, induced not by local lesions but by toxins from distant ones. There were no foci anywhere about the cord. Yet the cord was damaged. The clinical and pathologic picture of the cord was an exact counterpart of the subacute posterolateral sclerosis seen in pernicious anemia; Yet there could be no question here of a pernicious anemia; it was a typical and pure case of Hodgkin's disease.

It is usually admitted, but not often considered, that the so-called "pernicious anemia cord changes" are not specific to pernicious anemia. They may occur in other forms of anemias and cachexias by reason of similar but nonspecific toxic causes. In a recent review, Weil and Davison [18] insisted that only in hemolytic anemias is a real subacute combined degeneration ever found. They quoted in proof six cases of Hodgkin's disease. Four of these presented neurologic symptoms. Two of them came to autopsy, and in these two, a subacute combined degeneration was not found.

The condition is admittedly rare outside of pernicious anemia, but it does exist. In fourteen cases of Hodgkin's disease examined in our laboratory during the last year, this was the only one which showed a subacute combined degeneration. It appears just as undeniably in other conditions.

In a recent case of adenocarcinoma of the prostate gland, with generalized carcinomatosis, a slight secondary anemia and a severe cachexia, a flaccid paraparesis with sensory disturbance in the lower extremities and loss of sphincter control developed. At the autopsy a small carcinomatous metastasis was found in the posterior epidural space at the level of the second thoracic vertebra. It lay free in the epidural space and did not compress the cord; it did not even involve the dura mater. Nor was there even any reaction of the cord meninges to it. No arachnoidal cell masses were to be seen anywhere. Sections of the spinal cord at various levels, however, stained with sudan III, were almost exact duplicates of the cord in the second case of Hodgkin's disease described. The same, but less severe, symmetrical degenerative changes and accumulations of lipophages were to be seen in the posterior columns, in the dorsal spinocerebellar and in the lateral pyramidal tracts. More than one road leads to subacute combined degeneration.

Changes in the Skin.—Skin lesions in Hodgkin's disease are surprisingly frequent. According to various observers (Ziegler [19] and

18. Weil, A., and Davison, C.: Changes in the Spinal Cord in Anemia, Arch. Neurol. & Psychiat. **22**:966 (Nov.) 1929.

19. Ziegler, K.: Das maligne Lymphom, Ergebn. d. Chir. u. Orthop. **3**:37, 1911. Westphal, A.: Beitrag zur Kenntnis der Pseudoleukaemie, Arch. f. klin. Med. **51**:83, 1893.

Cole [20]), from 15 to 40 per cent of all cases show such lesions at some time or other. They may appear only long after, together with, or even long before the other manifestations of Hodgkin's disease (Bine [21]). They may be nonspecific, without characteristic histology, or specific, with the typical microscopic picture of lymphogranuloma.

The nonspecific lesions are by far the most frequent. They include (Fox [22]): (1) simple pruritus; (2) prurigoid lesions; (3) eczema, urticaria, erythema, papules and vesicles; (4) hemorrhagic and bullous eruptions; (5) exfoliating erythrodermias; (6) pigmentations, alopecia, change of nails; (7) acanthosis nigricans, and (8) lichenification.

Specific skin lesions are much less common. Cases have been reported by various investigators, including Trimble,[23] Beitzke,[24] Mulzer [25] and Caussade.[26] The histology has been described by Arzt,[27] Grosz,[28] Fox [22] and others, as typically the same as that of any Hodgkin's granuloma. The difficulty of clinical differentiation from mycosis fungoides and the aleukemic leukemias has been discussed by Highman,[29] Galloway [30] and Alderson.[31] They form nodules almost anywhere on the skin, are deep or superficial, may or may not ulcerate, are clean or secondarily infected, and may or may not itch. They develop from the preexisting reticulolymphatic tissue of the skin. The papillae are flattened. There is a diffuse and focal infiltration of the corium from the subpapillary plexus to within the subcutaneous fat, of histiocytes, giant cells, lymphocytes and eosinophils. Biopsy of such a lesion may

20. Cole, H. N.: The Cutaneous Manifestations of Hodgkin's Disease, J. A. M. A. **69**:341 (Aug. 4) 1917.

21. Bine, R.: Hodgkin's Disease of the Skin and Mucous Membranes, Am. J. M. Sc. **173**:503, 1927.

22. Fox, H.: Lymphogranulomatosis of the Skin in Hodgkin's Disease, Arch. Dermat. & Syph. **2**:578 (Nov.) 1920.

23. Trimble, W. B.: Pseudoleukemia Cutis, J. Cutan. Dis. **37**:336, 1919.

24. Beitzke, H.: Demonstration von Praeparaten eines multiplen megakaryozytischen Granuloms, Verhandl. d. deutsch. path. Gesellsch. **12**:224, 1909.

25. Mulzer, P., and Keining, E.: Ueber die bei Sternberg-Paltaufscher Krankheit vorkommenden spezifischen und besonders unspezifischen Hauptprozesse, Dermat. Ztschr. **53**:438, 1928.

26. Caussade, G., and Surment, J.: Granulomatose maligne, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:762, 1928.

27. Arzt, L.: Beitraege zur Differenzierung der granulomatoesen Hauterkrankungen, Acta derm.-venereol. **1**:365, 1920.

28. Grosz, S.: Ueber eiene bisher nicht beschriebene Hauterkrankung (Lymphogranulomatosis Cutis), Beitr. z. path. Anat. u. z. allg. Path. **39**:405, 1906.

29. Highman, W. J.: Lymphogranuloma, Mycosis Fungoides and Kindred Conditions, Arch. Dermat. & Syph. **13**:522 (April) 1926.

30. Galloway, J.: Remarks on Hodgkin's Disease, Brit. M. J. **2**:1201, 1922.

31. Alderson, H.: Cutaneous Metastases in Hodgkin's Disease, J. Cutan. Dis. **35**:481, 1917.

give the diagnosis of Hodgkin's disease long before there is any other warning of it (Miller [32]).

In the skin lesions in case 1 there was one feature, however, that I have not found described in any of the accounts of lymphogranulomatosis cutis. This was the strands of large, clear cells scattered in the corium between the granulomatous foci. These cells bore a striking resemblance to the "pseudoxanthoma" cells in chronic ovarian abscesses, in the wall of chronic salpingitis or chronic cholecystitis, in the angiomas associated with cerebellar cysts and in the interstitial tissue of a chronic nephrosis. They arose in the same way as swollen and proliferated histiocytes, stuffed with lipoid from adjacent broken-down tissue.

The Hodgkin's granulations had blocked off the local lymphatics of the corium, and invaded and destroyed the underlying fat tissue. The lymph stasis was desmoplastic, just as in filarial elephantiasis, and the sessile histiocytes proliferated. The lipoids of the fat tissue broken down by the granulomatous invasions were taken up by the sluggish lymph stream and absorbed by the proliferated histiocytes. The lipoid droplets themselves blocked lymph flow, and were themselves desmoplastic. A vicious cycle was thus set up until abundant strands of the pseudoxanthoma cells were formed.

Spleen.—In both cases there was neither gross nor microscopic evidence of splenic involvement. The prominence at times of the splenic enlargements—the often impressed descriptions of the colorful, "red porphyry" spleens—lead one to expect such involvement in all cases of Hodgkin's disease. As a matter of fact, in only about 15 per cent of the cases is the spleen enlarged enough to be palpable clinically (Desjardins [33]). Only 80 per cent of the cases show even slight involvement. In fully 20 per cent there is not even microscopic evidence of granuloma in the spleen.

Lung.—The lesion in the lung in case 1 was an exact reproduction of the clinical and gross anatomic picture of bronchogenic carcinoma. This unusual masquerade of Hodgkin's disease should be remembered in differential diagnosis.

The involvement of the lung in case 2 was an example of one of the possible, fantastic, local sequelae of Hodgkin's disease. Lymphogranulomatous peribronchial nodes caused decubitus ulceration of the bronchi. Peribronchial abscesses were thereby formed, aspiration from which produced pneumonia.

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32. Miller, H. E.: Lymphogranulomatosis Cutis, Arch. Dermat. & Syph. **17:** 156 (Feb.) 1928.

33. Desjardins, A., and Ford, F.: Hodgkin's Disease and Lymphosarcoma, J. A. M. A. **81:**925 (Sept. 15) 1923.

Roentgen Therapy.—The eventual futility of roentgen therapy is an old story. The literature reports variable results. In both of the cases described, the patients had extensive treatment to no avail. Although the involved lymph nodes melt away magically under roentgen therapy, they soon recur. With each recurrence they become more and more resistant to irradiation, until finally treatment with the x-rays is without effect. The average length of life from the onset of symptoms is just as long without roentgen therapy as with it.[34]

CONCLUSIONS

1. Hodgkin's disease may produce an epidural spinal tumor. Paraplegia follows from the production of a transverse degenerative myelopathy (so-called "transverse myelitis"). This transverse degenerative myelomalacia is produced at the level of the lesion, not by direct compression but by nonspecific arachnoid cell proliferation in the duraneural angles, which blocks the lymphatic drainage and causes lymph stasis in the cord.

2. Hodgkin's disease may also, without epidural foci, be responsible for the production of a subacute combined degeneration of the cord similar to that produced by pernicious anemia. In other types of anemia and cachexia the same condition may develop.

3. The specific cutaneous lesions of Hodgkin's disease are described with the development of "pseudoxanthoma" cells.

4. Splenic involvement may be absent even microscopically in Hodgkin's disease.

5. Pulmonary lymphogranulomatosis may simulate bronchogenic carcinoma. A complex sequence of involvement of the lung in another case is described.

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34. Wells, H. G.: Personal communication.

THE BLOOD ELECTROLYTE CHANGES IN NARCOSIS, WITH SPECIAL REFERENCE TO CALCIUM AND POTASSIUM

AN EXPERIMENTAL STUDY *

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The problem of narcosis is of interest from various standpoints. It interests, besides the surgeon and the anesthetist, the physician, on account of the similarity of the essential pharmacologic properties of narcotic and hypnotic drugs; both induce sleep, although of unequal depth, and, what is more important, of unequal duration. It also attracts the attention of biologists and psychologists who are interested in the problem of sleep.

The main purpose of this paper is to present the results of a study of the behavior of the electrolytic elements in the blood in sleep and in narcosis. The behavior of calcium and potassium during narcosis has been the main object of my investigation, because of the predominant part which, according to some investigators, these elements play in induced and natural sleep. Before recording the results of my investigations, I shall survey some studies that deal with narcosis, mainly on an anatomophysiologic basis.

THE METABOLISM DURING SLEEP AND NARCOSIS

1. *The Urinary Excretion.*—The essential observations concerning the urine during sleep and narcosis may be summarized as follows:

Elimination of urine, according to Piéron,[1] is lower during sleep than in the waking state. Elimination of phosphorus and ammonium is increased and excretion of chloride, total nitrogen, urea and amino-acids is decreased.[2]

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1. Piéron, Henri: Le problème physiologique du sommeil, Paris, Masson & Cie, 1913.

2. Lhermitte, J., and Tournay, A.: Rapport sur le sommeil normal et pathologique, Rev. neurol. **1**:761 (June) 1927.

A thorough study of urinary excretion during general anesthesia has been made recently by Stephen.[3] He found increased excretion of acid, urobilin, creatin, ammonia, amino-acids and urea and lowered elimination of total nitrogen. The increased elimination of neutral sulphur and cystine is attributed to the glutathione oxidation mechanism of cellular metabolism. He explained that glutathione is composed of glutamic acid and cystin and exists in two forms: (1) reduced and (2) oxidized. Hopkins and his co-workers, who isolated this substance, considered it as one of the main elements in tissue oxidation. Albumin has been found in the urine in 20 per cent of cases after chloroform anesthesia, and in all cases examined after ether anesthesia. Post-anesthetic acetonuria appeared to occur chiefly in nervous patients. With regard to the increased reducing power of the urine after anesthesia, Stephen questioned whether it is caused by glycosuria or by increased output of urochrome.

2. *Blood Chemistry.*—Investigations of the blood chemistry have reached results which point to definite changes in the electrolytic elements during narcosis. The changes in the content of calcium and potassium appear to have a particular significance.

Austin and his co-workers [4] found in ether anesthesia with acidosis a diminution of the total base, which is made up chiefly by a diminution of the base bound by proteins.

According to Mackay,[5] in general anesthesia the blood sugar rises steadily, the average increase being about 0.045 per cent in the first half hour and about 0.061 per cent in the second half hour.

Mackay and Dyke [6] noted, during general anesthesia in thirty-nine patients, distinct modifications in the distribution of chlorides between cells and plasma, changes in blood sugar content and in the carbon dioxide-combining power of the plasma. The chlorides increased in the plasma, whereas they remained unchanged in the whole blood. There is a "shift," using the authors' expression, of chloride ions from the red cells to the plasma. The carbon dioxide-combining power of the plasma fluctuates; it falls rapidly at the beginning of anesthesia, and then the decrease becomes slower and ceases altogether as the anesthesia proceeds. The blood sugar shows a rapid rise at the beginning of narcosis; later the rise becomes less pronounced and the blood sugar may reach nearly the starting level.

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3. Stephen, F.: Chemical Changes During Anesthesia, Brit. J. Anesth. **6**:109 and 187, 1928-1929.

4. Austin, T. H.; Cullen, G. E.; Gram, H. C., and Robinson, H. W.: The Blood Electrolyte Changes in Ether Acidosis, J. Biol. Chem. **61**:829, 1924.

5. Mackay, R. L.: Observations on Some Blood Sugar Changes in General Anesthesia, Brit. J. Anesth. **6**:15 (July) 1928.

6. Mackay, R. L., and Dyke, S. C.: On Certain Changes in the Blood During Surgical Anesthesia, Brit. J. Anesth. **6**:61, 1928.

The blood phosphates have been found increased during narcosis in man (five surgical cases) by Potter,[7] and in rabbits by Martland and Robison.[8]

Bolliger,[9] who has used ether, ethylene, chloroform, urethane, chloretone and other narcotics, noticed with a remarkable regularity a decrease of the inorganic blood phosphates.

Referring to studies concerned with the behavior of calcium and potassium in the blood during narcosis, I may quote first Cloetta and Thomann's [10] work. They made a thorough investigation of the specific weight, viscosity, content of different proteins, colloidal stability and surface tension of the blood plasma in dogs. This study failed to show significant changes, whereas in the same conditions the calcium and potassium contents of the blood had undergone definite deviations from the normal level. During sleep induced by ether, diethyl-diallyl-barbiturate of diethylamine and alcohol, in dogs, there was a fall of calcium of from 5 to 12 per cent. The deeper the sleep, the more pronounced was the decrease of calcium. As soon as the animal awoke, calcium returned to the original level. Potassium behaved in a reverse manner; it rose during narcosis and fell below the starting level when the animal awoke. This statement finds strong support in the observation made by Glaser and by Thomassen on man and also in the experiments on animals by Brauchli and Schnider.

Glaser [11] demonstrated that calcium in the blood diminishes from 15 to 20 per cent during hypnotic sleep. Thomassen [12] found a decrease of calcium in the blood during the state of depression and an increase in the manic state, in manic-depressive patients.

Brauchli and Schnider [13] came to the conclusion that a decrease of calcium, ranging from 5 to 8 per cent, takes place as soon as an animal falls asleep and that the rate of the decrease cannot be related to the duration of the sleep. Nor, in their opinion, does any proportional

7. Potter, D. G. E.: Changes in Blood in Anesthesia, Quart. J. Med. **18**: 261, 1925.

8. Martland, and Robison, R.: Note on the Estimation of Phosphorus in Blood, Biochem. J. **18**:768, 1924.

9. Bolliger: Phosphate Metabolism as Related to Anesthesia, J. Biol. Chem. **69**:721 (Aug.) 1926.

10. Cloetta and Thomann: Chemisch-physikalische Untersuchungen zur Theorie der Narkose, Arch. f. exper. Path. u. Pharmakol. **103**:260, 1924.

11. Glaser, F.: Psychische Beeinflussung des Blutserumkalkspiegels (über psychische Reaktionen), Klin. Wchnschr. **3**:1492, 1924.

12. Thomassen, H.: Psychische Beeinflussung des Serumcalciumspiegels, Klin. Wchnschr. **3**:2055, 1924.

13. Brauchli, E., and Schnider, O.: Ueber die Ionenverschiebungen im Blut bei Narkose und Erregungszuständen, Arch. f. exper. Path. u. Pharmakol. **119**: 240, 1927.

relation exist between the depth of sleep and the lowering of the calcium, since mild narcosis approaching the state of normal sleep is associated with a distinct diminution of calcium. Potassium does not behave in such a regular way. It shows a tendency to increase in deep narcosis, whereas in mild narcosis it may show a slight rise or no rise.

THEORIES OF NARCOSIS AND SLEEP

The so-called lipoid theory advocated by Meyer [14] and Overton [15] has been generally accepted as giving a satisfactory explanation of the action of narcotics. According to this theory, the narcotic property of the derivatives of methane is conditioned by their solubility in lipoids. Their effectiveness depends on their so-called "partition coefficient," which designates their comparative solubility in water and lipoids. Loewe,[16] on the ground of his investigations, believed that the lipoid theory should be modified in the sense that the lipoids adsorb narcotic substances instead of dissolving them; Zondek and Bansi [17] also introduced the notion of cell-adsorption into their theory of the rôle of the internal secretions in narcosis. The original idea was that different cells in a living organism are not at any time equally sensitive toward the products of internal secretion and ferments. The lowering of the cellular sensitiveness to hormones and ferments may be one of the conditions inducing sleep. With this idea in mind, the authors investigated whether, and to what extent, narcotics are able to interfere with the adsorption of epinephrine by animal charcoal. In a mixture of animal charcoal, water and epinephrine, 85 per cent of the latter was adsorbed. When alcohol was added to a similar mixture, nearly the whole amount of epinephrine (from 80 to 90 per cent) failed to be adsorbed. An analogous behavior of narcotics toward the adsorption of ovarian and thyroid hormones has been observed by Zondek. These observations led the authors to the belief that the essential property of narcotics is that of inducing important disturbances in cell permeability. Being easily adsorbed, narcotics interfere with the normal adsorption of hormones, and this is deemed to be the most important preliminary condition of both induced and natural sleep.

Beuttner [18] presented a theory, which finds ground in the teachings of Nernst and his co-workers, that stimulation is caused by changes in

14. Meyer, H.: Zur Theorie der Alkoholnarkose, Arch. f. exper. Path. u. Pharmakol. **42**:109, 1899.

15. Overton, E.: Studien über die Narkose, Jena, Gustav Fischer, 1901.

16. Loewe: Kritik der Meyer-Overtonschen Narkosetheorie, Deutsche med. Wchnschr. **38**:2387, 1912.

17. Zondek, H., and Bansi, H. W.: Hormone und Narcotica, Klin. Wchnschr. **6**:1319 (July 9) 1927.

18. Beuttner, R.: Eine rationelle Theorie der Narkose auf Grundlage elektromotorischer Wirkungen der Narcotica, Klin. Wchnschr. **7**:46 (Jan. 7) 1928.

the electric potential differences. Narcotic substances presumably inhibit these potential differences. This idea has been put to the test in an investigation of the action of narcotics on electromotivity in various artificial systems. It has been found that alcohol and ether, among other narcotic substances, provoke a more or less pronounced inhibition of the potential differences; that means inhibition of the stimulation to which living tissues are continuously subjected.

It will not be out of place to sketch here briefly the theories of sleep that share a common point with the theories of narcosis already referred to. Their common feature is that they do not refer the mechanism of sleep to any specific regulating center in the brain. Gaupp [19] considered sleep as a "psychophysical phenomenon." The psychic state plays the preponderant part; the lack of attention to the environment, the absence of any interest at the moment and consequently the lowering of the mental activity favor sleep, notwithstanding the lack of the feeling of fatigue. On the contrary, affective stimulation and intellectual overactivity will interfere with sleep, even when the subject feels tired physically. Goldscheider [20] also placed great emphasis on the importance of the psychic state. The lowering of the excitability of the cerebral cortex is a preliminary condition of sleep. Decreased excitability may result from the absence of adequate external stimuli or may be caused by a lasting stimulation leading to fatigue of the nerve cells. On the other hand, overstimulation, either physical or intellectual, may induce a more or less enduring state of excitement of the nerve cells which hinders sleep.

Pavlov,[21] on the basis of his studies of conditioned reflexes, came to the conclusion that internal inhibition and sleep are fundamentally identical processes. He stated that internal inhibition takes place when there is temporary weakness or complete disappearance of a well established conditioned reflex; this occurs when the conditioned stimulus is applied several times without being accompanied by the unconditioned stimulus with which it has been associated. If one continues to apply the conditioned stimuli notwithstanding the extinction of the conditioned reflex, drowsiness and sleepiness develop. This observation is in accordance with the general law that any stimulation acting on a certain spot of the cerebral hemispheres, if it is not associated with stimulation of other cerebral regions or if it does not alternate with other stimulations, leads inevitably, sooner or later, to drowsiness and sleep.

19. Gaupp, R.: Ueber Wesen und Behandlung der Schlaflosigkeit, Verhandl. d. Kong. f. inn. Med. **31**:9, 1914.

20. Goldscheider, A.: Ueber Wesen und Behandlung der Schlaflosigkeit, Verhandl. d. Kong. f. inn. Med. **31**:45, 1914.

21. Pavlov, T. P.: Lectures on Conditioned Reflexes, translated by W. H. Gantt and G. Volborth, New York, International Publishers, 1928.

This is well known and is generally expressed in the proposition: "Every monotonous and continuous stimulation leads to drowsiness and sleep." The cell inactivity in the form of sleep does not remain localized in the spot which has been subjected to repeated monotonous stimulations, but is spread over the hemispheres and the lower parts of the brain. The mechanism of this passage still remains obscure. One must, however, admit that exhaustion of the cells which, in Pavlov's opinion, is the underlying cause of sleep, brings forth a special substance or process inhibiting the activity of the cells involved and is carried over to other cells that have been spared during the stimulation which induced sleep. As to the distinction between inhibition and sleep, it may be characterized as follows: Inhibition is a partial, well localized sleep in a certain spot only; sleep, on the contrary, is an inhibition which has spread over the hemispheres and even the midbrain. Pavlov recorded experiments demonstrating the passage of inhibition into sleep and vice versa, the summation of separate inhibitory processes into sleep and the simultaneous disappearance of both. The theory of Pavlov deserves special consideration in view of the fact that it is founded on experimental investigation.

In contrast with the theories of sleep and narcosis that consider sleep as a general biologic and neurodynamic phenomenon involving primarily and predominantly the central nervous system are the investigations that point to the existence of specific centers regulating sleep:

Troemmer [22] pointed to the thalamus opticus as the organ of sleep. He excluded the spinal cord, the cerebellum and the cerebral cortex on the ground that destructive processes in these parts do not interfere with sleep. Nor has sleep been disturbed in decerebrated animals. Reasoning by exclusion, he admitted the location of the sleep center in the brain stem. The thalamus was chosen finally as the seat—the center, because it is the convergent center for the sensory stimuli closest to the cerebral cortex.[23]

Economo,[24] notwithstanding the fact that he considered sleep as a complicated biologic phenomenon comprising specific modifications in all organic functions, admitted the existence of a sleep regulating center in the diencephalon. The rôle of this center is to regulate the normal periodic changes from the waking state to sleep. This function is a vegetative one, and it shares with other vegetative functions the com-

22. Troemmer, E.: Physiologie und Psychologie des Schlafes, Neurol. Centralbl. **29**:438, 1910.

23. See the criticism of this theory by Nachmansohn, D.: Zur Frage des Schlafzentrums, Ztschr. f. d. ges. Neurol. u. Psychiat. **107**:342, 1927.

24. von Economo, C.: Ueber den Schlaf, Vienna, Julius Springer, 1925; Schlaftheorie, Ergebn. d. Physiol. **28**:312, 1929 (reprint from T. F. Bergmann, Munich).

mon property of being specifically influenced by certain limited areas in the central nervous system. Mueller [25] also located the sleep center in the diencephalon. One may seek support for the assumption of the existence of specific sleep centers in studies which point to a selective, hypnotic action of various drugs on different regions of the brain.

Molitor and Pick [26] demonstrated in experiments on rabbits the reenforcing hypnotic action of certain combinations of drugs. The reenforcing action of urethane, for instance, when added in a small, otherwise ineffective dose to paraldehyde and chloretone, is particularly striking since it almost doubles the duration of sleep. In the author's opinion, one deals here with a selective action of the drugs on different parts of the brain.

The studies of Mehes [27] showed that scopolamine and morphine, to which rabbits are only slightly sensitive, induced sleep easily in these animals when they were decerebrated. From these experimental investigations and the anatomopathologic studies in man, Mehes concluded that the regulatory sleep center is located in the brain stem, namely, in that part of the hypothalamus which is close to the aqueduct of Sylvius. When the stimulating influence of the cerebral hemispheres is removed by decerebration or weakened by drugs, sleep is more easily obtained through the action on the aforementioned sleep centers.

The part that the thalamus plays in sleep has also been indicated by experiments in which, after the removal of both the cerebral hemispheres and the corpora striata (Schoen, Jamawaki, quoted by Pick [28]), hypnotics remained effective; in some animals, they provoked sleep even in subnormal doses. In a review of the literature discussing the rôle of the cortex and the brain stem in sleep, Pick [28] suggested that one may distinguish two groups of narcotics: (1) cortical and (2) thalamic.

Keeser and Keeser [29] showed, in a series of experiments on rabbits, that when barbital, phenylethyl-barbituric acid and diallyl-barbituric acid are injected intravenously, they are to be found chiefly in the thalamus, in lesser amounts in the striate bodies and not at all in the cerebral hemispheres, mesencephalon, cerebellum, pons varollii or medulla

25. Mueller, L. R.: Die Lebensnerven, Vienna, Julius Springer, 1924.

26. Molitor, H., and Pick, E. P.: Verstaerkte Schlafmittel-Wirkung durch gleichzeitige Behandlung verschiedener Hirnteile, Arch. f. exper. Path. u. Pharmakol. **115**:318, 1926.

27. Mehes, J.: Studien über den Angriffspunkt von Schlafmitteln, Wien. klin. Wchnschr. **39**:962 (Aug. 19) 1926.

28. Pick, E. P.: Ueber Schlaf und Schlafmittel, Wien. klin. Wchnschr. **40**: 634, 1927.

29. Keeser, E. and T.: Ueber die Lokalisation des Veronals, der Phenyl-äethyl- und Diallylbarbitursäure im Gehirn, Arch. f. exper. Path. u. Pharmakol. **125**:251, 1927; Ueber den Nachweis von Caffein, Morphin und Barbitursäure derivaten im Gehirn, ibid. **127**:230, 1927.

oblongata. In another series of experiments, they demonstrated that when caffeine was injected even in so small a dose as 0.1 mg. per kilogram of weight, it could be detected everywhere in the brain; morphine has been revealed in a relatively great amount in the diencephalon, and less in the cerebral hemispheres; none was present in the midbrain, pons varolii, medulla oblongata or cerebellum; also in these rabbits the derivatives of barbituric acid were found to have a selective localization in the brain similar to that in the first series of rabbits.

The contribution made to the problem of sleep by Demole [30] appears to be of particular interest on account of the method used and the striking results obtained. The starting point of his studies was the hypothesis formulated by Cloetta and Thomann, that calcium, while diminishing in blood during sleep, accumulated in the brain tissue. The intracerebral injection of a few decimilligrams of calcium chloride in twenty-four cats induced in each more or less pronounced sleep. The depth and the duration of the sleep were dependent on the dose. With 0.00025 Gm. of calcium chloride, sleep lasted from thirty to sixty minutes; with 0.002 Gm., it lasted for three hours. The solution of calcium chloride was colored and thus could be located on anatomic examination. The latter led the author to conclude that the para-infundibular region, which is between the oral, the suprachiasmal and the caudal part of the infundibulum (tuber cinereum and adjacent parts), should be considered as the sleep area (Schlafzone). The main interest of Demole's work does not lie, I think, in the determination of the seat of a sleep center, for it seems to me that the conception itself of the existence of a specific center regulating sleep can be justly criticized. The significance of the investigation by Demole and Cloetta-Thomann lies mainly in the part that the calcium metabolism takes in the phenomenon of sleep.

The hypothesis propounded by Cloetta and Thomann, that the decrease of the calcium content in the blood during narcosis coincides with its increase in the brain, appears to find strong support in Demole's work, for the introduction of calcium chloride into the brain tissue in cats invariably induced sleep, whereas the introduction of potassium chloride into the same cerebral region was followed by a state of restlessness, stupor, muscular rigidity and epileptoid convulsions. It seemed to me, therefore, worthwhile to submit the calcium metabolism in sleep to a new experimental test.

My experiments were carried out on rabbits. For narcosis I used in a few animals ether, and in most of them diallyl-barbituric acid

30. Demole, V.: Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:229, 1927.

(dial). Control experiments were performed in the same rabbits which had served for narcosis. Care was taken to carry out all experiments under similar conditions. The handling of the specimens of blood was identical in all my investigations.

PROCEDURE AND METHODS OF ANALYSIS

Blood obtained by heart puncture was taken in a dry pyrex tube. Within from one-half to one hour after the puncture, the blood was centrifugated and the serum removed. For the adequate determination of potassium, it is imperative to have the serum removed from the cells within two or three hours following the puncture, on account of the higher amount of potassium in the cells and its passage into the serum. In my investigations, when serum remained in contact with the cells for more than four or five hours an increase of potassium in the serum was noticeable. After the contact of a few days (from three to seven days in my tests), the quantity of potassium was twice or three times as great as the original amount.

For the determination of calcium in serum the Clark and Collip[31] modification of the Kramer and Tisdall method was used. The deviations inevitable with this method may be, according to the authors, within the limits of ±3 per cent. My experience with the method corroborates these observations.

Potassium was estimated by Kerr's[32] technic, which is a modification of the method of Kramer and Tisdall. Kerr admitted that the technical errors may go as far as ±5 per cent. In my tests of the method, deviation within the limits of ±7 per cent could hardly be avoided.

In the analyses for inorganic phosphates, I used Benedict and Theis'[33] modification of Briggs' method. Magnesium was determined by Briggs' method.[34]

The carbon dioxide-combining power of the plasma was estimated by the procedure of Hawk and Bergheim[35] (van Slyke and Cullen's method). It should be noted that for these analyses blood was drawn from the veins of the ear. In my experience on the occasion of another study,[36] it was found that the carbon dioxide-combining power of specimens of blood taken from the heart within short intervals may vary a great deal, whereas in similar conditions there are no significant changes when blood is taken from the ear.

BLOOD CHEMISTRY (CALCIUM AND POTASSIUM) DURING SLEEP INDUCED BY ETHER

Ether was used as a means of inducing sleep in ten experiments. Specimens of blood were taken before ether was administered and dur-

31. Clark and Collip: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:43, 1925.

32. Kerr: Studies on the Inorganic Composition of Blood, J. Biol. Chem. **67**: 689, 1926.

33. Benedict and Theis: J. Biol. Chem. **61**:63, 1924.

34. Briggs, A. P.: Some Applications of the Colorimetric Phosphate Method, J. Biol. Chem. **59**:255, 1924.

35. Hawk and Bergheim: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Company, 1927.

36. Katzenelbogen, S.: The Action of Histamine on the Alkali Reserve, J. A. M. A. **92**:1240 (April 13) 1929.

ing sleep, from five to thirty-five minutes after the beginning of sleep. No appreciable changes in calcium content of the blood were found in two experiments; in four, the changes were within the limits of + 2 and — 3 per cent, which are the limits of error allowed by the method. In two animals, the decrease was slight (— 3.1 and — 3.6 per cent) being on the border line of the limits of error allowed by the technic. Only in two experiments were significant changes found (— 4.5 and — 9.4 per cent). When one tries to find a reason for the heterogeneity of these results, which are the more striking since in each experiment blood was taken during sound sleep of the animal, one may find a certain relation between the duration of sleep and the rate of change in the calcium content. As a matter of fact, the greatest fall of calcium was observed in the two animals in which the sleep was longest, and in the single experiment in which an increase of calcium was found the animal had slept only five minutes when the blood was drawn. These data, not being conclusive per se on account of the small number of observations, suggested further investigations which will be described later.

Potassium was determined in four animals only; in each I found a decrease, ranging from — 8.5 to — 26.6 per cent, with an average of — 17 per cent. I mention without comment that the slightest decrease took place in the two animals the sleep of which endured the longest.

BLOOD CHEMISTRY (CALCIUM AND POTASSIUM) DURING SLEEP INDUCED BY DIALLYL-BARBITURIC ACID

In fifty-eight experiments performed on forty-one rabbits, diallyl-barbituric acid was used to induce sleep. The rabbits weighed from about 2 to 3 Kg. Diallyl-barbituric acid was given either intravenously or intramuscularly, in doses ranging from 0.8 to 1.75 cc., depending on the size of the animal and the length of sleep which I desired to obtain. Samples of blood were taken before the drug was administered and again, during sleep, at different periods of time varying from one to fourteen hours (in one experiment twenty-one hours) after the beginning of sleep.

Calcium and potassium were determined in each of the fifty-eight experiments, whereas the carbon dioxide-combining power of the plasma, inorganic phosphorus and magnesium were estimated in ten experiments only. The modifications which calcium underwent during the induced sleep displayed a marked uniformity. In fifty of fifty-eight experiments (86.2 per cent), the calcium content of the blood decreased, the difference between the starting level and that during sleep being from — 3.5 to — 29.9 per cent, with an average of — 11.1 per cent. In three experiments no changes were found. In five, the changes were within the limits of error allowed by the method (less than — 3 per

cent), but it is interesting to note that also in these experiments the changes consisted in a reduction of calcium. One meets thus with the fact that in 55 of 58 experiments the calcium content of the blood fell during sleep.

Potassium was determined in fifty-one experiments. Changes within the limits of technical error were noted in nine experiments (17.6 per cent). An increase was found in five experiments (9.8 per cent), ranging from + 15.1 to + 79 per cent. A decrease was found in thirty-six experiments (70.6 per cent), ranging from — 7.6 to — 50.9 per cent, with an average of — 17.7 per cent. In one experiment, the potassium content went up after two and one-half hours' sleep and fell below the starting level after five hours' sleep. One sees that the behavior of potassium during sleep does not show the uniformity that characterizes the behavior of calcium. There is, however, a marked predominance of the cases (70.6 per cent) in which a distinct decrease was found.

In ten experiments, in addition to analyses for calcium and potassium, determinations of the carbon dioxide-combining power of the plasma, inorganic phosphorus and magnesium were made. The alkali reserve went down during sleep in three animals, within the limits of — 16.7 to — 22.7 per cent; and increased in five experiments, in the range from + 11 to + 93 per cent. No change was found in two experiments.

In the estimation of inorganic phosphorus during the induced sleep, no appreciable modifications were found in three animals, an increase was evident in one, and a decrease in six, of from — 15.9 to — 32 per cent.

The changes of the magnesium content followed closely those of the phosphorus content. No significant change was found in one experiment, the difference between the starting level and that during sleep being 0.2 mg. only, though the change in percentage appears to be great (+ 15.1) on account of the small absolute amounts found. An increase was noted in two (+ 21 and + 60 per cent), and a decrease in six experiments, of from — 11.9 to — 34.5 per cent.

CONTROL EXPERIMENTS

A control investigation was carried out on thirty-seven rabbits chosen from among those which had been used for narcosis. Specimens of blood were taken at intervals ranging from twenty minutes to twenty-four hours. The animals remained fasting as they were during the experiments with diallyl-barbituric acid. Calcium was determined in forty-two experiments. No changes beyond the limits of technical error were found in thirty-three experiments (78.6 per cent). A slight increase took place in one and a decrease in eight experiments.

Potassium was estimated in forty-three experiments. No changes greater than the limits of error allowed by the method (7 per cent) were found in eighteen experiments (41.9 per cent). More or less appreciable deviations from the starting level were found in twenty-five experiments, ranging from — 33 to + 28.5 per cent. Of this number, 15 (34.9 per cent) showed a decrease ranging from — 8.4 to — 33 per cent, with an average of — 16.6 per cent, while ten (23.2 per cent) showed an increase ranging from + 7.2 to + 28 per cent, the average being + 15.8 per cent.

In ten control experiments, in addition to calcium and potassium, the carbon dioxide-combining power of the plasma, inorganic phosphorus and magnesium were determined. The carbon dioxide-combining power in four experiments showed a decrease of from — 13 to — 23.4 per cent. An increase was found in two experiments, of + 9.1 and + 10.8 per cent, and no change in four. Magnesium showed a decrease in two experiments, of — 10.3 per cent and — 25 per cent. An increase was found in three experiments, of from + 18.8 to + 25.5 per cent, and no appreciable changes in four experiments. As to inorganic phosphorus, it increased in two rabbits, fell in three and did not change in five.

COMMENT

Study of the blood chemistry during narcosis as compared with that in control experiments justifies the following statements:

The carbon dioxide-combining power of the plasma did not show entirely characteristic changes during narcosis. There was, however, an increase in five of ten experiments, whereas in the control study only two of ten experiments showed an increase. A decrease was found in three narcotized rabbits as compared with four of the control rabbits; no changes were noted in two rabbits as against four of the controls.

The inorganic phosphorus showed a tendency to decrease in narcosis; it fell in six of ten rabbits, whereas in the control experiments three of ten showed a decrease. These data corroborate the observations of Bollinger [9] and contradict those of Potter [7] and Robison.[8] The changes in the magnesium content follow closely those in the phosphorus content; a diminution was found in six of ten experiments as compared with two of ten control experiments. It should be noted that I do not attribute a conclusive significance to the modifications of the three elements just considered, because of the small number of experiments in which they were investigated. A more substantial ground for conclusions will be found in a study of calcium and potassium metabolism, since these two elements were subjected to a relatively extensive investigation.

Potassium was found (chart 1) to decrease in thirty-six of fifty-one experiments (70.6 per cent). An increase was noted in five experiments

(9.8 per cent), and no appreciable change in nine (17.6 per cent). The control study, performed on forty-three rabbits included a predominant number in which no significant changes were found, eighteen of forty-three (41.9 per cent) and ten (23.2 per cent) in which an increase was found. My observations disagree with those of Cloetta and Thomann,[10] who found regularly an increase of potassium during narcosis. Notwithstanding the prevalence in my study of the experiments

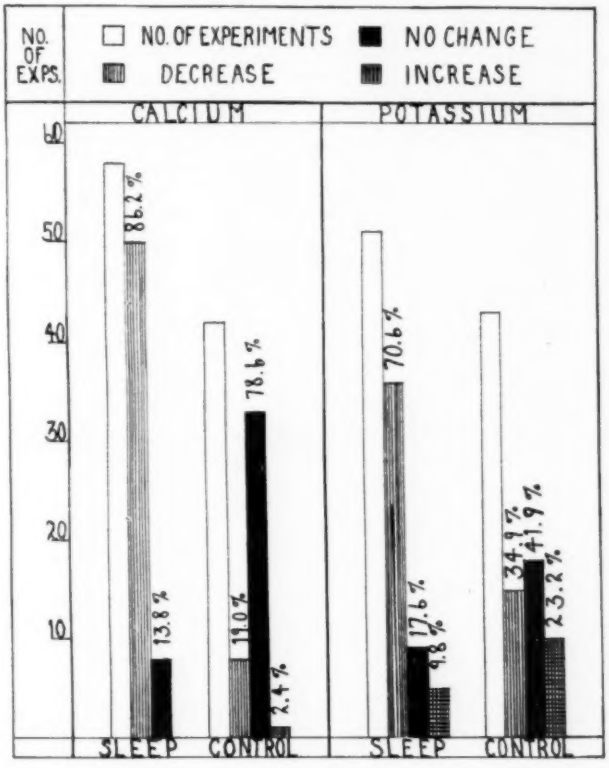

Chart 1.—The changes in the calcium and potassium contents of the blood of rabbits during narcosis. No special column was made for the one experiment in which an increase of potassium was found after two and one-half hours and a decrease after five hours' sleep.

displaying a decrease of potassium, I do not conclude that a fall of potassium in the blood is characteristic of narcosis. To draw such a conclusion would be hardly fair in view of the high percentage of cases with a decrease of potassium in the control experiments. I feel justified rather in believing that potassium does not behave in a regular characteristic way in narcosis. This conclusion finds support in the investigation by Brauchli and Schnider,[13] who stated that potassium shows a

tendency to increase in deep narcosis, whereas in mild narcosis it may show no rise or a very slight one.

In contrast with these relatively heterogeneous data, I found a striking homogeneity in the modification of calcium during narcosis (chart 1). In fifty-five of fifty-eight experiments, calcium went down during sleep. Taking into consideration the rate of the decrease and bearing in mind the unavoidable technical errors within the limits of ± 3 per cent, I still found an appreciable decrease in fifty out of

TABLE 1.—*Comparison of Changes in Calcium Content of the Blood in Normal and Narcotized Rabbits*

Rabbit	Changes in Calcium Content, per Cent	
	Control	During Sleep
28	+ 3.5	—10.2
28	—10.2	—17.4
29	—13.9	—19.2
34	—13.7	—16.7
26	—10.0	—19.2
43	— 4.1	— 7.2

TABLE 2.—*Relation of the Change in the Calcium Content of the Blood in Narcosis to the Duration of Sleep*

Experiment	Duration of Sleep, Hours	Changes Calcium, per Cent	Duration of Sleep, Hours	Changes Calcium, per Cent
1	5	— 8	10	—13.1
2	5	0	10	— 2.4
5	6	0	11	—13
6	4	— 5.8	6½	— 6.2
7	5½	— 7.6	10½	— 8.2
9	6	— 5.5	11½	—13
10	5½	— 4.2	11	— 5.1
12	4¼	—10.7	12¼	—27.4
13	6	— 6.5	11	— 6.5
14	3½	— 1.5	11½	—12.5
17	6	—10.2	12	—11.2
20	2½	— 5.5	5	—17.9
39	2½	— 6.6	10½	—13.2
40	1¼	— 1.5	10¼	— 9.6
41	1¼	— 2.1	10¼	— 2.8

fifty-eight experiments (86.2 per cent), ranging between —3.5 to —29.9 per cent, with an average of —11.1 per cent.

When these results are compared with those in the control experiments, one finds that in the latter, forty-two experiments, no changes were found in thirty-three (78.6 per cent), a slight increase in one and a decrease in eight (19 per cent). A spontaneous diminution occurred in my animals when the blood was taken the second time, in about 20 per cent, instead of 86.2 per cent as was found during narcosis in the same animals. It is noteworthy that of the nine animals in which spontaneous changes of the calcium content occurred, greater modifications, always in the sense of a decrease, took place in six animals when they were sleeping, although blood was drawn at the same intervals in both series of experiments. This may be seen from table 1.

I come to the conclusion that a fall of calcium content is characteristic of narcosis, in complete agreement with Cloetta and Thomann,[10] and Brauchli and Schnider.[13] There is, however, one point that I do not share with Brauchli and Schnider. These authors claimed that a decrease of calcium takes place as soon as the animal falls asleep, and that the rate of the decrease is not related to the duration of sleep. My investigation shows that such a relation exists. It was suggested

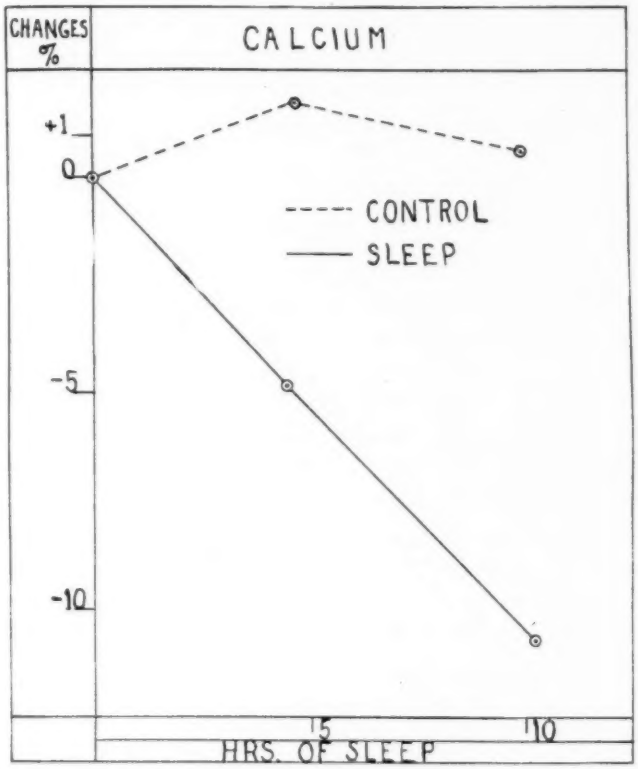

Chart 2.—Relation of the change in the calcium content of the blood in narcosis to the duration of sleep. The hours of sleep and the changes of calcium are averages of fifteen experiments in which sleep was induced and six control experiments.

at first by experiments with ether narcosis in which the short duration of sleep coincided with a small decrease or with hardly any significant change in the calcium content. In one experiment, when the animal slept six hours, no significant change in the calcium content was found (— 2.7 per cent). The experiment using the same animal was repeated on two occasions, but blood was taken eleven and one-half hours after the beginning of sleep; the changes of calcium were: — 14.2 and

— 19.2 per cent. A more thorough study of this relationship is to be found in table 2, giving the results of experiments in which blood was taken at two different intervals during sleep. The data show that in fourteen of fifteen experiments, the longer the sleep, the greater the decrease of calcium (chart 2). Such an absolute interrelation is not to be found when one considers sleep in different animals. They do not react in a similar way, and after an equal duration of sleep the deviation of the calcium content from the starting level differs in various rabbits; still a relative proportionality exists, since the lowest levels of calcium are much more frequent in the animals with a long narcosis than in those with a short one.

The data pointing to a decrease of calcium in the blood during sleep and the hypnotic effect of calcium when introduced into the brain tissue (Demole) suggest further investigations along the following lines: (1) a comparative study of the content of calcium in different regions of the brain in animals in which sleep was followed by death; (2) the combined administration of calcium and hypnotics with the idea that the effect of the latter will be reinforced through a shift of calcium from the blood into the brain tissue.[37]

SUMMARY AND CONCLUSIONS

1. The blood chemistry was investigated in rabbits during narcosis induced by ether in ten animals and by diallyl-barbituric acid in fifty-eight experiments carried out on forty-one rabbits.

2. The carbon dioxide-combining power of the plasma, inorganic phosphorus and magnesium were studied in ten experiments.

3. A control study was carried out on thirty-seven rabbits chosen from among those which had been used for narcosis.

4. The potassium content of the blood during narcosis was investigated in fifty-one and the calcium content in fifty-eight experiments.

5. The carbon dioxide-combining power of the plasma increased in five of ten experiments. In the control experiments, two of ten showed an increase.

6. The inorganic phosphorus showed rather a tendency to decrease in narcosis; it went down in six of ten experiments. In the control experiments, three of ten showed a decrease.

7. The changes in the magnesium content during narcosis followed closely those in the phosphorus content; a diminution was found in six of ten experiments, as compared with two of ten in the control experiments.

8. Potassium was found to decrease in thirty-six of fifty-one experiments (70.6 per cent), as compared with fifteen of forty-three control

37. These investigations are being carried out in Phipps Clinic.

experiments (34.9 per cent). An increase was found in five experiments (9.8 per cent) and no marked changes in nine (17.6 per cent) during narcosis.

9. Calcium decreased during sleep in fifty-five of fifty-eight experiments. In five there was a small decrease (within the limits of possible technical error, $\pm$ 3 per cent); in three no change was found. An appreciable decrease was noted in fifty of fifty-eight experiments (86.2 per cent).

10. I do not attribute a conclusive significance to the modification of carbon dioxide-combining power, phosphorus and magnesium because of the small number of experiments in which they were investigated.

11. I conclude that potassium does not behave in a characteristic way in narcosis.

12. A decrease of calcium is characteristic of narcosis. There is a distinct relation between the rate of the decrease of calcium and the duration of sleep. In fourteen of fifteen experiments, the longer the sleep the greater was the decrease of calcium.

THE INCIDENCE OF FEVER AND LEUKOCYTOSIS IN MULTIPLE SCLEROSIS *

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The diagnosis of multiple sclerosis is seldom made without certain generally recognized difficulties. Yet the obstacles encountered in attempting to arrive at a definite knowledge of the etiologic factors concerned are considerably greater. Few reports have been made of observations on clinical aspects of the disease other than those of a strictly neurologic nature. Certain other details of clinical expression may possibly aid in rendering a diagnosis less difficult and in determining a course that might lead to a solution of the problem of etiology.

This study was undertaken in order to determine whether the review of a fairly large series of cases might not reveal one or two clinical facts the incidence of which might render them of value. Accordingly, all the clinical records at the Peter Bent Brigham Hospital of cases that were classed as multiple sclerosis were reviewed. It might be well to point out here that these records offer a distinct advantage for a study of this kind. The staff is unusually unified, because many separate departments do not exist. All patients are admitted directly to a general medical or surgical department, where each is thoroughly studied from a general point of view. After these general observations, consultation is sought from the proper sources.

In larger hospitals, in which patients are admitted directly to one of many distinct departments, the records are apt to reflect rather restricted and specific points of view.

One hundred and forty-nine records were found in which the diagnosis of multiple sclerosis was made. Of these 109 were selected in which the complete clinical, neurologic and special examinations (including complete studies on the spinal fluid) rendered the diagnosis unquestioned both at the time of observation and in retrospect. It was interesting to note that of these cases, forty-five, or 41.3 per cent, were referred to Dr. Cushing's neurosurgical clinic as tumor of the brain or of the spinal cord was suspected. The remainder were admitted to the medical department, and, in the majority of instances, their condition was defi-

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* From the Medical Service, Peter Bent Brigham Hospital.
* Work done under Multiple Sclerosis Fund of Harvard University.
* From the Department of Neuropathology, Harvard Medical School.

nitely diagnosed as multiple sclerosis after consultation with the neurosurgeons.

In the review of these cases it was noted that during hospitalization a considerable number of the patients exhibited abnormalities of body temperature and of leukocyte count. It is therefore to the occurrence and incidence of these two abnormalities that particular attention is paid in this paper. Although other facts were also noted, such as the incidence of various neurologic signs and symptoms, age, sex, nationality, etc., their repetition was not considered necessary, as they agreed closely with similar figures of other series. The record of each patient who had had an abnormal temperature or leukocytosis was scrutinized carefully in order to determine whether there was any evidence of the generally recognized causes of such signs. If such was the case, the temperature was disregarded and classified as normal.

There is always likely to be some controversy as to the dividing line between normal and abnormal temperatures. It is a recognized fact that certain normal activities may cause distinct variations in the body temperature, such as muscular exercise, exposure to heat and cold and other conditions affecting metabolic processes. However, under constant conditions of muscular inactivity such as are attained by hospitalized patients such factors may be safely disregarded, and then even a slight elevation in temperature must be attributed to some pathologic process. Samson Wright [1] stated that the normal temperature of the body varies between 96.7 and 99 F. by mouth. Cannon and other physiologists of this country have not found the upper limit as high, but state that the normal range is between 96.7 at 4 or 5 a. m. and 98.6 F. about 4 p. m. Macleod [2] stated that in man the normal temperature varies a few tenths of a degree about 37 C. (98.6 F.). Rectal temperatures are usually about 1 degree higher than those obtained by mouth and are rather more accurate. According to Macleod,[2] however, if the thermometer is left in the mouth for two or three minutes and kept under the tongue with the mouth closed, affecting conditions such as air circulating in the mouth during respiration, the previous ingestion of warm or cold foods, etc., are overcome, and the temperature agrees closely with the rectal. Wright [1] cited Fishberg's experiment in which the latter immersed two dozen thermometers in a bath of warm water and found readings between 98.2 and 102.6 F. For a batch of more expensive thermometers the readings varied between 98 and 105.4 F. In this country, however,

1. Wright, Samson: Applied Physiology, London, Oxford University Press, 1926.

2. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, St. Louis, C. V. Mosby Company, 1926.

certificated thermometers only are employed in all hospitals, thus rendering such errors extremely unlikely.

In the Peter Bent Brigham Hospital temperature readings are taken by mouth unless contraindicated for obvious reasons. Thermometers are left in the mouth for at least three minutes and usually longer. In the series of records reported here temperatures were recorded every four hours in the great majority of instances. In view of these facts, it was concluded that any elevation to or above 99 F. for two or more consecutive days could be regarded as abnormal.

The study of these records from this point of view showed (table) that of the total number of 109 cases of multiple sclerosis, only forty-eight, or 44.1 per cent, showed normal temperature. The remaining sixty-one, or 55.9 per cent, showed abnormal elevations in temperature—that is to say, rises to or above 99 F. on two or more days during hospi-

Number and Percentages of Cases of Multiple Sclerosis with Fever and Leukocytosis

	Number of Cases	Percentage of All Cases	Percentage of Patients With Fever	Number of Cases With Leukocytosis	Percentage of Cases With Leukocytosis
Normal temperature	48	44.1	....	4	8.1
Abnormal temperatures					
99 to 99.5 F	49	44.9	80.3	18	36.7
99.5 to 100 F	12	11.0	19.7	3	25.0
Total abnormal	61	55.9	100.0	21	34.4
Total	109	....	....	25	22.9

talization. Of these sixty-one cases with abnormal temperatures, forty-nine, or 80.3 per cent, were between 99 and 99.5 F.; fifteen, or 24.6 per cent, were above 99, and eight, or 16.5 per cent, reached 99.5 F. Twelve of the sixty-one cases, or 19.7 per cent, showed temperatures varying between 99.5 and 100 F.; three cases, or 4.9 per cent of the total number with abnormal temperatures, showed an elevation to 100 F. No cases were found with temperature readings above 100 F. In other words, then, in a total of 109 records studied, 44.1 per cent showed normal temperature charts; and in 55.9 per cent the temperature was abnormal, i. e., 99 F. or above, 44.9 per cent reaching levels between 99 and 99.5 F., and 11 per cent between 99.6 and 100 F. Chart 1 shows the approximate number of cases at each degree of abnormal temperature. Chart 2 shows the actual temperature records in three cases.

The observation of a number of cases in this series with leukocytosis was also interesting and significant. Again there arose the difficulty of determining at just what point a leukocyte count may be considered abnormal. The normal variation is generally considered between 5,000

and 10,000, while a count between 10,000 and 12,000 arouses slight suspicion. Above the latter level a leukocytosis might be considered definitely abnormal if a physiologic cause is not present. Physiologic leukocytosis seldom exceeds 12,000 or 14,000 (Todd and Sanford [3]). According to most authors, leukocytosis may occur in the newly born as high as 18,000; in pregnancy during the ninth month; during labor, averaging 18,000 in primiparae; during exercise, and after cold baths. Garrey and Butler [4] recently pointed out that leukocyte counts should be made under conditions which eliminate all physiologic variations and that the

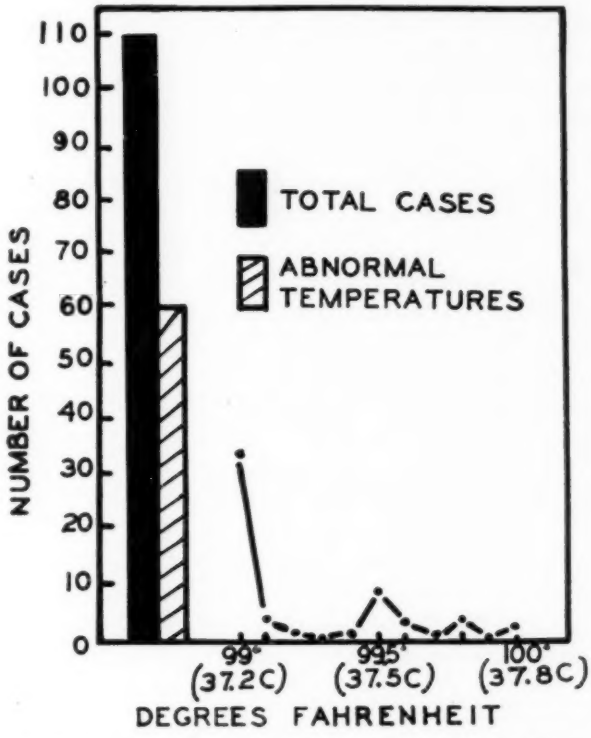

Chart 1.—Proportion of multiple sclerosis with abnormal temperature and the number of cases at each degree.

results should be evaluated as a deviation from a basic norm. They found that this basic condition was attained by absolute rest in the recumbent position, when the count reaches its lowest level within an

3. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1928.

4. Garrey, W. E., and Butler, Virginia: Basal Leucocyte Count and Physiological Leucocytosis, Proc. Staff Meet., Mayo Clin. **4**:157 (May 15) 1929; Physiological Leucocytosis, Am. J. Physiol. **90**:2 (Oct.) 1929.

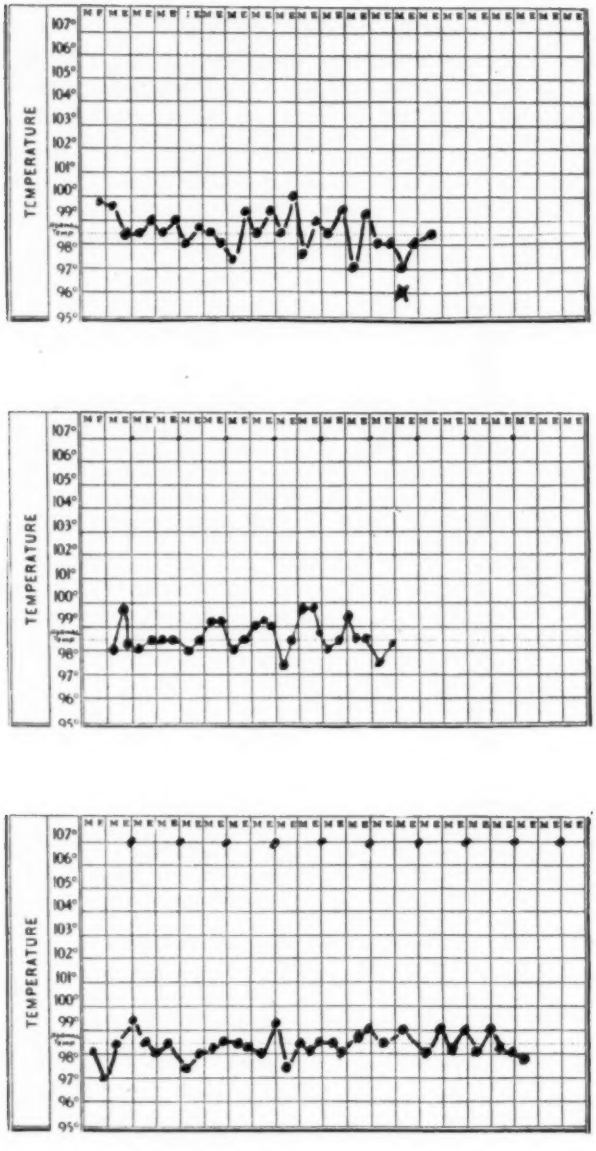

Chart 2.—Reproductions of actual temperature records in three cases of multiple sclerosis.

hour and is maintained as long as the patient remains quiet. Ninety-five per cent of the basal counts were between 5,000 and 6,000, a few reaching 7,000. In subjects working under conditions of ordinary activity the count was between 8,000 and 10,000. Mild degrees of exercise raised the count to 12,000 or 13,000, but the basic norm was regained in fifteen minutes. They found that pain may raise the count considerably, but they denied absolutely any physiologic variation during digestion.

As a general rule, the conditions under which leukocyte counts are done in hospital wards approximate those set down by Garrey [4] for the attainment of a basic norm. At the Brigham Hospital they are done at least one or two hours after the patient has been put to bed unless emergency dictates otherwise. The patients whose records were studied here were confined to bed during their stay in the hospital, so that blood counts were done under conditions of rest and recumbency. It was therefore considered that for this study a leukocyte count above 11,000 could be considered abnormal.

The result of the study of these 109 records from this point of view showed that in twenty-five, or 22.9 per cent, there was a leukocytosis varying between 11,000 and 18,000. In four, or 3.6 per cent, of these patients the temperature remained normal. The count was 11,000, 13,000, 15,000 and 18,000, respectively. The remaining twenty-one cases were accompanied by abnormal temperatures, but the leukocytosis was not proportionate to the degree of elevation in temperature. The highest count, 18,400, was derived from the blood of a patient whose temperature did not exceed 99 F.; the three patients whose temperatures reached 100 F. had counts of 12,060, 12,450 and 14,200, respectively.

Information concerning the incidence of both abnormalities can be had from an analysis of the accompanying table, which reveals that only forty-four cases, or 40.4 per cent of the total, showed neither leukocytosis nor elevation in temperature; forty cases, or 36.7 per cent, showed abnormal temperatures alone; four, or 3.6 per cent, showed leukocytosis alone; and twenty-one, or 19.3 per cent, showed both fever and leukocytosis. In eighteen of the latter, or 16.5 per cent, the leukocytosis accompanied temperatures the high level of which varied between 99 and 99.5 F., while in three, or 2.8 per cent, the temperatures were between 99.6 and 100 F.

A third interesting and significant fact was also noted in the course of this study. Nineteen cases, or 17.4 per cent, were found in which a pleocytosis of the spinal fluid was recorded. Of these, three showed normal temperatures and leukocyte counts, seven were accompanied by fever alone and seven by both fever and leukocytosis. Ayer and Foster [5]

5. Ayer, J. B., and Foster, H. E.: Multiple Sclerosis, New York, Assn. for Research in Nerv. & Ment. Dis., 1921.

found increased cell counts in the cerebrospinal fluid in many cases that were beyond doubt, and in the nineteen cases mentioned here the diagnosis seemed unquestionable. It is true that in the majority of these cases the cell counts were only slightly above normal and might be accounted for by errors in technic. On the other hand, several were as high as 30 and one was recorded at 70. Ayer, in forty-eight specimens, found from 0 to 5 cells in 61.2 per cent of the cases; from 6 to 10 cells in 16.7 per cent; from 11 to 20 cells in 4.2 per cent, and 42 cells in 2 per cent.

COMMENT

The striking incidence shown in these figures justifes the conclusion that every case of multiple sclerosis may at some time or other exhibit febrile changes and leukocytosis. An effort was made to determine whether these reactions were coincidental either with the onset or with a fresh exacerbation of symptoms. The obvious disadvantages of dealing with past records alone rendered this point practically impossible to decide. However, it was evident that practically all the patients came to the hospital because of the beginning of the disease or of fresh symptoms. Since these reactions are likely to occur during the most active stages of the disease, and since many patients are seen when this stage is passed, one might infer that every case shows similar reactive changes at some time or other.

Sachs [6] conceded that a febrile movement may play a part in the earliest stages of the disease, but he did not think that such an observation would help to establish the diagnosis. On the contrary, he thought that it would arouse some suspicion as to the validity of a diagnosis of multiple sclerosis. The evidence given here shows that reactive changes of temperature and blood do play a part in many cases, although it can hardly be expected that they could serve as diagnostic criteria. On the other hand, the observation of such facts in cases in which the condition had already been diagnosed correctly gives some suggestions as to the nature of the etiologic factors.

It has always been the general opinion that fever and leukocytosis are indicative of a reaction to toxic or infectious agents. In the absence of any of the known causes of these changes, it must be assumed that they are due in these cases to the disease process of multiple sclerosis and therefore that the etiologic factors concerned in this disease are of a toxic or infectious nature. However, another possibility must be considered, namely, that such febrile changes are dependent on degenerative changes in or about thermic centers in the brain. It has long been thought that definite heat centers exist in the cerebrum, destruc-

6. Sachs, B.: Multiple Sclerosis, New York, Assn. for Research in Nerv. & Ment. Dis., 1921.

tion of which would lead to a disturbance in body temperature as in the hyperthermia of "medullary edema" following cerebral operations. Kornblum [7] was unable to confirm the existence of such a center and concluded that such hyperthermia is not dependent on a lesion of any definite area of the brain but on disturbance of widely distributed reflex arcs essential to the maintenance of body temperature. He also stated that the fever might be accounted for by toxins reaching the cerebrospinal fluid from the sudden destruction of brain cells or from altered function of the choroid plexus. In many of these cases of multiple sclerosis the elevation in temperature was accompanied by leukocytosis, an occurrence which is rarely seen in the hyperthermia of so-called "medullary edema."

These data, then, are presented merely as facts from which no definite conclusion can be drawn at present. However, in any disease certain clinical facts might turn attention toward a certain group of etiologic factors. The observations reported here might well lead one to consider more seriously those factors of a toxic or an infective nature.

SUMMARY

1. The study of 109 records of reasonably certain cases of multiple sclerosis is reported with reference to the reactive changes in temperature, leukocyte count and examination of the cerebrospinal fluid.

2. Forty and four-tenths per cent showed neither fever nor leukocytosis, but three showed increased cell counts in the cerebrospinal fluid.

3. Fifty-five and nine-tenths per cent showed elevations in temperature, 44.9 per cent between 99 and 99.5 F. and 11 per cent between 99.6 and 100 F.

4. Twenty-two and nine-tenths per cent showed definite leukocytosis, 3.6 per cent occurring without elevation in temperature and 19.3 per cent accompanying febrile reactions.

5. Pleocytosis of the cerebrospinal fluid occurred in nineteen cases, or 17.4 per cent; three of these cases showed normal temperatures and leukocyte counts; seven were accompanied by fever alone; two by leukocytosis alone, and seven by both fever and leukocytosis.

7. Kornblum, Karl: A Clinical and Experimental Study of Hyperthermia, Arch. Neurol. & Psychiat. **13**:754 (June) 1925.

GALACTOSE TOLERANCE IN DEMENTIA PRAECOX*

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During the course of a diagnostic and therapeutic survey of dementia praecox at the Worcester State Hospital, a series of one or more determinations of the galactose tolerance in 135 untreated male patients has been accumulated. The group constitutes a fairly representative cross section of the male schizophrenic population in such an institution. The ages range from 16 to 63 years, the periods of hospitalization from one week to twenty-three years.

This study of the galactose tolerance is a part of a larger study directed toward an attempt to secure further light on two major problems: Are there any metabolic peculiarities by which the schizophrenic psychosis can be characterized? Within the schizophrenic group, are there any characteristic metabolic differences among the various subgroups? Such differences, if present, would be of obvious aid in differential diagnosis and of possible prognostic value.

THE GALACTOSE TEST

The galactose tolerance test has been selected as the best practicable index of carbohydrate tolerance in general. As Rowe [1] emphasized, the test has certain practical advantages over other types of carbohydrate tests in common use. Since galactose appears in the urine with relatively low dosage, it is possible to determine the upper limits of tolerance even in patients in which this is high. Especially in marked instances of pituitary deficiency, the tolerance threshold may be so high as not to be reached with ordinary sugars without the administration of dosages that, in themselves, significantly interfere with the digestive processes, causing vomiting or diarrhea. As regards other low threshold sugars, such

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1. Rowe, A. W.: Metabolism of Galactose: Threshold of Tolerance in Normal Adults, Arch. Int. Med. **34**:388 (Sept.) 1924.

as the pentoses, disadvantageous factors are excessive cost, difficulty of securing sufficiently pure supplies, and the possibility of these sugars acting as other than food products. Galactose, on the other hand, is a product with which the human organism is accustomed to deal from earliest infancy.

The secretion threshold rather than the blood sugar curve has been selected as a criterion because of the unreliability of the latter. As shown by Hansen [2] and independently by Albritton [3] several years ago, the blood sugar level in the individual subject varies rather strikingly from moment to moment, even when the rate of sugar intake is kept rigorously constant by means of a Woodyatt pump. Straight line interpolations, therefore, between points at fifteen minute or half-hour intervals may be entirely misleading as regards the individual subject. In a statistical compilation, such errors presumably cancel each other, permitting the detection of mass trends, but for specific diagnostic purposes blood sugar curves, no doubt, frequently lead to errors. It is unfortunate that the fundamental papers of Hansen and Albritton have been so generally overlooked by clinical writers in this field.

One of the theoretical objections to the use of galactose given by the oral route as a test for sugar tolerance is the variation possible in its absorption rate. Disturbances in gastro-intestinal motility or the functional condition of the mucosa might affect the rate in either direction. This, however, is a disadvantage common to all carbohydrate tests except those in which the sugar is injected by vein. Another objection is that changes in renal permeability, either functional or organic, may influence the threshold for sugar. Folin and Berglund [4] stated that the sugar excretion observed after very small doses of galactose clearly points to the absence of a renal threshold for this sugar. Rowe [5] did not agree with this conclusion in its entirety and offered several objections to the statement. Whether or not Folin and Berglund were correct, in an absolute sense, the test is practically not vitiated if care is used to avoid the collection of unduly dilute or concentrated urine for the determinations. One then need merely define the threshold as the lowest amount of reducing substance that will give a detectable positive reaction with a suitable standard reagent.

In this paper, no cases are presented in which the patients have shown kidney defects, as far as can be determined by means of urinalysis, including nitrogen partition determinations, and phenolsulphonphthalein tests. Blood chemistry determinations were carried out in all cases, and no deviations from the normal were detected that were sig-

2. Hansen: Acta med. Skandinav. **58**:372, 1923.
3. Albritton: Am. J. Physiol. **69**:548, 1924.
4. Folin and Berglund: J. Biol. Chem. **51**:213 (March) 1922.
5. Rowe and Chandler: Endocrinology **8**:803 (Nov.) 1924.

nificant as regards this particular problem. Spatial limitations preclude more detailed consideration of these topics, but an elaborate critique of galactose metabolism in general can be found in the recent publications by Rowe.[6]

CARBOHYDRATE METABOLISM IN DEMENTIA PRAECOX

Several workers have studied the metabolism of sugar in dementia praecox, utilizing blood sugar curves rather than urinary estimations as an approach to the problem. Kooy[7] studied ten cases of the hebephrenic type showing autism, loss of real interest in daily life, a high degree of suggestibility and negativism and incomprehensible associations in speaking and acting. He administered test meals of 100 Gm. of bread and butter and 200 cc. of milk. He used Bang's method of dextrose determination. Three-quarters of an hour after the meal, the sugar curve was found to be higher than normal.

Raphael and Parsons[8] reported eleven cases of dementia praecox in which they gave a test meal of 1.75 Gm. of dextrose per kilogram of body weight, each gram of dextrose being dissolved in 2.5 cc. of distilled water. No glycosuria was reported. In seven of the cases, all of which were in an acute phase, the initial fasting level was lower than normal. The acme was relatively high and the return to the primary level required more than three hours, marking a definite delay. In two other cases, the curve was of the same general shape as that in the seven cases already noted, except that the acme was higher. In one case of several years' duration, the patient showed a normal curve. These writers concluded that tolerance curves in dementia praecox differ from those in normal subjects, and that the tolerance curves vary according to the clinical phase of the disorder.

Lorenz[9] used the same technic (Janney-Isaacson) in a group of fifty-two cases of dementia praecox, subdivided into the following types: twenty-five hebephrenic, eleven catatonic, nine paranoid and seven simple deteriorating. He found that the patients in active catatonic

6. Rowe (footnote 1). Rowe and Chandler (footnote 5). Rowe, A. W.: Sugar Tolerance as Aid to Diagnosis, J. A. M. A. **89**:1403 (Oct. 22) 1927. Rowe: Endocrinology **12**:1 (Jan. and Feb.) 1928. Rowe and Lawrence: ibid. **12**:245 (May and June) 1928; 377 (July and Aug.) 1928; 591 (Sept. and Oct.) 1928; 707 (Nov. and Dec.) 1928; **13**:1 (Jan. and Feb.) 1929; 109 (March and April) 1929; 263 (May and June) 1929. Rowe: ibid. **13**:327 (July and Aug.) 1929.

7. Kooy: Brain **42**:214 (Oct.) 1919.

8. Raphael, T., and Parsons, J. P.: Blood Sugar Studies in Dementia Praecox and Manic-Depressive Insanity, Arch. Neurol. & Psychiat. **5**:687 (June) 1921.

9. Lorenz, W. F.: Sugar Tolerance in Dementia Praecox and Other Mental Disorders, Arch. Neurol. & Psychiat. **8**:184 (Aug.) 1922.

phases of the disease responded to dextrose feeding with a hyperglycemia similar to that obtained in cases of hyperthyroidism. Several subjects with simple deteriorated dementia praecox responded to dextrose feeding in a manner that resembled the response obtained, according to Lorenz, in certain endocrine disturbances, such as dyspituitarism.

Bowman, Eidson and Burlage,[10] in a study of ten cases of schizophrenia, found a tendency toward a sustained blood sugar curve. Three subjects gave normal curves and three sustained curves. Two subjects who gave a sustained curve at the first examination showed a normal curve at a second examination six months later.

Barrett and Serre[11] studied twenty cases: nine hebephrenic, five paranoid and six catatonic. They found a great variety of sugar curves, but none that could be termed typical or of constant occurrence. After repeating the tests in ten cases, they found that although the patients had apparently remained in the same condition the second curve in most cases differed greatly from the first. This is precisely what one would expect, however, from the work of Hansen and Albritton previously referred to. Barrett and Serre stated that their observations showed that no constant relation between dementia praecox and sugar tolerance has as yet been observed, and that if a relation exists it is seemingly influenced by factors which create fluctuations in sugar metabolism that at times allow large quantities to be disposed of and at other times depress the processes of sugar disposal.

Henry and Mangam[12] found that dextrose curves in nine acute cases of dementia praecox, mostly paranoid, were similar to those reported by Lorenz and by Raphael and Parsons. The patients were given 0.8 Gm. of dextrose dissolved in 2 cc. of water per pound of body weight. The juice of one lemon was added to make the solution more palatable. They concluded that their observations in acute cases indicated a definite depression of the functions of the vegetative nervous system.

Kasanin,[13] using the technic of Janney and Isaacson, determined the blood sugar curves of forty patients with schizophrenia. Seven were discarded on account of the presence of somatic factors that might influence the curve. Of the thirty-three remaining cases, twenty-two were classified as abnormal, nine showed a "high curve," seven a "low curve" and eleven normal curves. In his cases he found no curve characteristic of this group of conditions. He collected one hundred and fifty-four cases from the literature and found the average curve

10. Bowman, Eidson and Burlage: Boston M. & S. J. **187**:358 (Sept. 7) 1922.

11. Barrett and Serre: J. Nerv. & Ment. Dis. **59**:561, 1924.

12. Henry, G. W., and Mangam, E.: Blood in Personality Disorders. Biochemical Studies, Arch. Neurol. & Psychiat. **13**:743 (June) 1925.

13. Kasanin, J.: Blood Sugar Curve in Mental Disease: Schizophrenic Groups, Arch. Neurol. & Psychiat. **16**:414 (Oct.) 1926.

well within the normal limits, although the percentage of abnormal curves was much higher than in healthy subjects. He also noted that the observations of the various authors were not consistent with each other. Patients in a stupor usually responded with a high sustained sugar curve, although normal curves as well might be found in stuporous patients.

Drury and Farran-Ridge,[14] using Calvert's method for blood sugar determinations, in eighteen cases of dementia praecox gave a sugar dosage of 50 Gm. of medicinal dextrose dissolved in 150 cc. of water. They found a profusion of different types of curves, which made an analysis extraordinarily difficult. Patients in an acute stage gave very high and rather broad curves. In chronic cases, there was a tendency toward small low curves. The curves in female patients were higher than those in males in both acute and chronic cases.

Bowman [15] determined twenty-two blood sugar curves in a series of twenty-four cases of schizophrenia in which he made endocrine biochemical studies. He stated: "It is difficult to define the limits of the normal blood sugar curve with any degree of precision, but, roughly, twelve cases showed a normal curve, nine cases showed a high, sustained type of curve, and one case showed a reversed type of curve."

A consideration of the foregoing evidence as a whole, with due regard to the "spontaneous" fluctuations of the blood sugar level reported by Hansen and by Allbritton as of common occurrence in the individual case, leads to the conclusion that after a dextrose meal the blood sugar tends to remain high for a longer than normal period. This, in turn, indicates that dementia praecox is characterized by a depression of the mechanisms regulating the maintenance of carbohydrate equilibrium.

Comparatively little work has been done with galactose as a means of studying carbohydrate metabolism in mental disorders. Hirose,[16] Strauss,[17] Wagner [18] and others noted a depressed tolerance for galactose in neuroses. Rowe also noted a lowering of the tolerance in various neuroses and psychoses.

Bowman [15] reported nineteen cases of dementia praecox in which he gave the normal adult tolerance dose (Rowe) of galactose, 40 Gm. in females or 30 Gm. in males. Fourteen of his patients were females and five were males. Eight of the female patients gave a positive reaction in excess of 0.3 Gm. All of the patients tested, however, showed a demonstrable melituria during the test, and it is probable that some of the tests would also have been positive with smaller doses of galactose. Bowman mistakenly attributed to Rowe the interpretation

14. Drury and Farran-Ridge: J. Ment. Sc. **71**:8 (Jan.) 1925.
15. Bowman: J. Nerv. & Ment. Dis. **65**:465 (May) 1927; 585 (June) 1927.
16. Hirose: Deutsche med. Wchnschr. **38**:1414, 1912.
17. Strauss: Neurol. Centralbl. **32**:1281, 1913.
18. Wagner: Ztschr. f. klin. Med. **80**:174, 1914.

that 0.3 Gm. of sugar appearing in the urine indicates a decreased gonadal function. According to Rowe's definition of the galactose tolerance level,[19] all of Bowman's cases were positive. We are unable to tell definitely whether the tolerance in these cases was raised, lowered or normal. In the interpretation of such observations, the carbohydrate paradox is involved; i. e., an increase in the dose above the assimilation limit does not necessarily produce a proportionate elimination of the excess.

TECHNIC

Rowe's technic[20] for the performance of the galactose tolerance test has been used in all cases. The tolerance for galactose was defined by Rowe as that dose of the material which, under standard conditions of administration, will uniformly produce a transitory melituria detectable by a dependable and sensitive reagent (Benedict's), while a similar dose, a few grams (from 5 to 10) less in amount will be equally unproductive. He further stated that "obviously the true tolerance level lies between the two amounts. Its more exact determination will be a most time-consuming operation and might well introduce the influence of minor factors and variations that are now absorbed in the present simple tests."

In a careful and elaborate study of galactose metabolism, Rowe found that the average tolerance for normal men is 30 Gm. For normal women, in adult years to the menopause, it is 40 Gm.; prior to puberty, it is 20 Gm.; with the establishment of the catamenia, it passes to 30 Gm., and at maturity reaches 40 Gm. The precautions recommended by Rowe in carrying out the test were observed.

1. The sugar must be very pure to prevent leakage through the kidney of foreign reducing material capable of absorption but not of utilization. Pfanstiehl's galactose, of the highest purity obtainable, was used throughout. 2. The sugar must be dissolved in pure water only, and the patient should be in a basal state. 3. The oral route is best as it is simplest, and the possible error from variation in the rate of absorption has been shown not to be significantly large. 4. The patient must be in good nutritional equilibrium before the test is made. 5. Muscular effort and extremes of heat and cold are to be avoided during the test. Keeping the patient in bed during observation is to be recommended. About one half of our patients were kept in bed during the test. It was found to be unnecessary to go to this length with the balance of the patients, as they were quiet and tractable. 6. Since renal injury may introduce a source of error, the level of kidney function should be determined. Benedict's test was used throughout in testing for reducing bodies.

In fairness, it should be stated that Rowe's observations on galactose tolerance are at variance with those of certain other workers in this field. Von Noorden[19] stated that the assimilation capacity of men for galactose

19. Von Noorden: Die Zuckerkrankheit, Berlin, A. Hirschwald, 1910, cited by Rowe.

20. Rowe (footnote 6, third reference).

is 20 Gm.; Hirose [16] assumed the tolerance to be 25 Gm.; Strauss,[17] 30 Gm., and several others, 40 Gm. It is possible that the different conclusions were due to a failure on the part of the several authors to recognize the sex difference recorded by Rowe or to the use of impure galactose.

RESULTS

The summarized results of our study are set forth in table 1, and analyzed in succeeding tables and charts. In most instances, only a single determination was made before the patient was placed under treatment. In a certain number of cases, however, two or more initial determinations were made. A report of the effects of endocrine and

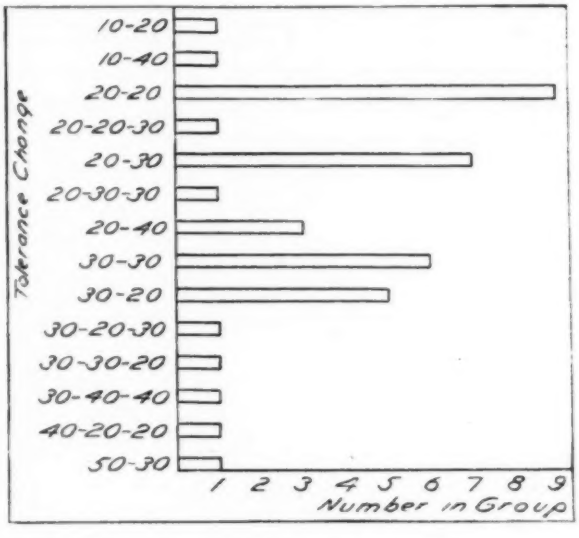

Fig. 1.—Variability of galactose tolerance in thirty-nine cases of dementia praecox in which two or more tests were made.

other types of therapy on the galactose tolerance is reserved for subsequent publication.

Variability of the Threshold in the Individual Patient.—As is shown in figure 1, there is a certain amount of variability in thresholds in the same patient at different times. Fifteen patients gave the same reaction in all tests. In twenty-four cases, the threshold varied. Since the thresholds are determined by gradations of 10 Gm. in dosage, it happens that in the tabulations there is a preponderance of multiples of ten. However, when more than one test was available, the average was taken and tabulated to the nearest five. In figure 2 is shown the distribution of thresholds in the total series of patients. Each threshold determina-

TABLE 1.—*Primary Data*

Name	Diagnosis*	Date Admitted	Age at Test, Years	Date of Test	Weight at Test, Kg.	Period in Hospital, Months	Test Positive, Gm.	Blood Sugar, Mg. per 100 Cc.	Total Nitrogen, Gm.	Creatinine Nitrogen, Gm.
G. A.	H	6/ 9/23	30	2/ 6/29	55.0	68	10	100	8.2	0.36
L. A.	H	1/30/26	25	9/ 6/27	58.0	10	50	91	8.3	0.32
				3/13/28	58.3	25	30	82	10.1	0.48
H. A.	H	1/ 8/26	31	11/14/27	65.2	22	20	95	....	....
W. A.	U	5/ 5/23	30	1/22/29	65.0	68	20	94	10.6	0.44
A. A.	C	5/23/23	23	5/25/28	50.8	60	20	91	....	....
L. A.	U	6/ 7/22	21	9/—/27	55.4	62	20	91	9.5	0.41
				3/26/28	54.5	69	30	100	11.6	0.40
W. B.	U	7/19/29	29	7/31/29	60.3	12 days	30	111	5.5	0.35
A. B.	U	1/28/29	21	2/12/29	57.0	1	30	90	8.3	0.45
				4/ 2/29	54.4	3	30	99	9.6	0.48
B. B.	C	7/24/28	30	9/ 8/28	52.2	1	30	91	9.6	0.37
M. B.	U	11/21/22	31	6/18/29	....	78	20	119	12.1	0.49
				10/12/29	....	82	20	100	10.3	0.40
A. B.	S	8/16/27	36	10/19/28	54.4	14	30	82	15.1	0.50
P. B.	C	3/29/29	24	6/26/29	....	3	30	77	....	....
A. B.	C	7/ 3/29	23	7/22/29	60.9	19 days	30	105	13.5	0.46
C. A.	U	5/26/27	28	11/21/27	54.8	6	30	102	8.8	0.43
				3/20/28	57.0	10	40	..	8.1	0.38
				3/28/28	....	10	40	..	9.6	0.39
E. B.	C	1/27/28	20	4/25/28	48.4	3	40	118	....	....
A. C.	U	5/16/29	27	7/24/29	55.2	2	20	94	7.9	0.49
F. C.	U	9/ 4/28	26	11/15/28	45.0	2	30	82	7.6	0.36
W. C.	U	8/15/27	35	4/ 2/28	59.4	8	30	111	9.9	0.36
L. C.	S	7/12/21	31	7/22/29	41.0	96	20	83	10.8	0.38
M. C.	U	7/10/28	27	11/16/28	60.4	4	40	93	11.5	0.42
D. C.	..	1/20/27	21	4/ 2/28	....	15	20	..	7.4	0.38
C. C.	P	4/ 9/28	22	5/ 8/28	58.6	1	30	103	9.8	0.45
				10/12/28	56.0	6	30	122	9.8	0.42
V. C.	H	1/14/28	16	8/20/28	62.0	7	30	89	11.1	0.40
F. C.	S	12/27/26	23	7/31/29	66.4	7	40	94	12.3	0.42
C. D.	S	3/22/28	39	4/26/28	46.0	1	10	105	7.3	0.38
E. D.	S	4/15/21	29	7/ 2/29	51.2	98	20	102	7.8	0.40
A. D.	C	12/15/28	24	3/11/29	44.0	3	30	87	....	....
P. D.	U	7/27/28	43	7/24/29	57.2	12	20	91	8.7	0.49
T. D.	H	4/19/28	31	6/ 7/28	70.6	2	40	95	....	....
J. D.	H	11/ 7/21	30	11/14/27	63.2	72	20	80	10.0	0.54
				3/14/28	65.6	76	20	83	....	....
O. D.	P	1/11/26	45	3/26/29	63.5	38	20	89	13.0	0.49
J. F.	U	3/29/23	37	9/—/27	60.6	53	40	87	....	....
				3/26/28	60.8	50	20	85	....	....
				8/31/28	61.6	64	20	78	15.2	0.48
F. F.	H	5/17/18	30	7/ 3/29	62.8	133	20	105	12.2	0.45
J. F.	U	6/20/27	30	8/—/27	71.4	2	20	85	7.6	0.49
				11/14/27	69.2	5	30	..	11.0	0.51
F. F.	U	10/ 9/28	31	7/ 3/29	54.6	9	20	104	8.8	0.43
A. F.	H	3/27/28	27	4/16/28	80.8	20 days	30	100	6.7	0.50
				5/ 4/28	79.6	1	20	87	4.4	0.35
R. G.	P	6/ 4/27	33	9/30/27	70.0	3	20	95	11.8	0.46
J. G.	U	6/28/28	39	9/ 8/28	73.1	3	30	105	13.0	0.49
				11/20/28	74.6	5	20	118	....	....
S. G.	U	12/12/28	40	6/12/29	54.4	6	20	111	9.2	0.37
A. G.	H	4/ 9/28	26	5/10/28	65.5	1	10	100	8.1	0.38
H. G.	P	5/ 8/28	45	4/13/29	52.6	11	20	84	8.6	0.35
J. G.	H	3/19/25	38	7/26/29	49.4	52	10	91	....	....
				9/24/29	49.4	54	40	118	10.8	0.49
D. G.	P	11/15/28	37	7/16/29	57.2	8	20	105	8.5	0.42
E. H.	S	3/ 6/25	37	7/31/29	54.0	52	20	99	....	....
E. H.	U	10/ 9/24	35	7/16/29	71.3	57	20	103	7.3	0.38
J. H.	H	4/22/21	28	7/15/29	51.0	98	20	111	....	....
				9/ 3/29	51.0	100	40	91	....	....
J. H.	H	3/ 7/07	49	7/22/29	46.7	268	20	98	11.7	0.38
R. H.	P	9/29/24	39	5/25/28	56.4	43	30	105	6.0	0.35
A. H.	U	8/24/28	37	11/15/28	54.6	3	50	87	9.4	0.40
R. H.	S	3/ 4/27	27	4/ 4/27	....	1	20	125	....	....
J. H.	H	5/15/28	22	5/29/28	40.0	14 days	30	133	8.9	0.41
T. H.	C	11/ 5/26	29	7/—/27	....	8	30	122	....	....
				11/ 7/27	65.8	12	30	111	....	....
E. J.	P	2/ 9/26	37	9/—/27	....	19	20	95	....	....
				11/ 7/28	55.0	33	30	100	10.2	0.48
				11/27/28	55.4	33	30	105	10.3	0.46
D. I.	C	10/ 2/23	39	1/17/28	48.6	51	20	83	....	....
				3/21/28	51.0	53	30	79	17.0	0.39
A. J.	C	9/29/27	22	6/25/28	60.4	9	20	80	....	....
A. J.	P	2/18/29	27	6/26/29	62.2	4	20	94	11.9	0.48
P. J.	P	1/24/23	32	1/17/28	64.0	48	30	100	8.1	0.42

* C, H, P, S and U indicate catatonic, hebephrenic, paranoid, simple and unclassified types, respectively.

TABLE 1.—*Primary Data—Continued*

Name	Diagnosis*	Date Admitted	Age at Test, Years	Date of Test	Weight at Test, Kg.	Period in Hospital, Months	Test Positive, Gm.	Blood Sugar, Mg. per 100 Cc.	Total Nitrogen, Gm.	Creatinine Nitrogen, Gm.
W. K.	P	7/12/27	34	6/26/29	90.3	21	30	91	11.4	0.52
B. K.	P	1/23/28	26	7/29/29	59.2	18	30	87	7.2	0.47
J. K.	C	3/28/28	23	4/26/28	67.4	1	30	95	14.5	0.55
J. K.	S	10/29/16	56	9/—/27	39.1	142	30	91	....	....
				11/ 7/27	38.3	144	30	91	....	....
C. K.	P	5/26/27	29	6/12/29	53.2	24	20	110	7.6	0.36
D. K.	U	6/10/27	17	9/—/27	62.2	3	20	105	6.9	0.36
H. K.	U	2/23/20	28	2/ 5/29	52.0	107	10	76	10.4	0.44
E. K.	H	1/25/29	21	2/12/29	52.0	8 days	20	89	....	....
				7/15/29	55.6	6	30	75	....	....
F. L.	U	11/26/26	19	7/10/29	54.8	31	40	90	10.4	0.47
N. L.	H	4/ 7/25	29	4/ 6/29	54.8	47	20	93	9.4	0.43
R. L.	H	2/ 5/29	31	7/10/29	48.4	125	20	103	8.0	0.41
				10/ 2/29	45.8	128	20	83	....	....
E. L.	H	10/ 6/28	41	7/15/29	51.8	9	5	118	8.8	0.35
D. M.	P	2/28/28	33	4/16/28	59.0	2	30	98	10.9	0.49
J. M.	P	4/26/16	51	7/15/29	64.4	158	20	111	9.4	0.36
				10/ 7/29	62.1	161	20	...	9.0	0.54
A. M.	S	2/16/16	37	7/24/29	54.4	148	20	100	....	....
				9/ 4/29	54.2	150	20	118	....	....
T. M.	H	2/ 9/27	23	6/11/29	53.2	28	20	123	9.6	0.43
				9/24/29	56.2	31	30	105	....	....
C. McC.	H	3/17/27	18	7/—/27	....	4	20	111	7.8	0.45
T. McD.	H	11/28/23	23	1/22/29	45.0	61	20	86	12.1	0.39
				2/19/29	45.0	62	20	..	....	....
				4/24/29	44.8	64	30	109	9.9	0.46
B. McE.	H	6/ 3/28	32	9/ 8/28	60.9	3	20	105	9.5	0.49
A. McF.	U	7/ 7/27	35	7/29/29	62.0	24	10	102	....	....
E. McM.	S	8/ 7/17	33	11/14/27	66.2	123	30	78	10.2	0.53
B. M.	H	10/16/28	16	12/11/28	49.0	2	30	114	....	....
				2/27/29	52.8	4	30	95	....	....
G. M.	H	1/24/25	29	5/25/28	64.3	40	30	105	9.7	0.45
M. M.	P	8/ 4/25	47	3/27/29	68.2	42	20	104	9.1	0.40
D. M.	U	9/11/27	24	4/16/28	44.1	7	20	72	....	....
G. M.	U	10/19/22	30	1/18/28	71.6	62	30	80	9.0	0.54
				3/21/28	....	64	30	89	12.4	0.50
				5/ 1/28	74.4	66	20	100	....	....
J. N.	H	8/18/27	33	3/14/28	60.0	7	10	83	11.3	0.43
W. N.	C	3/ 3/26	23	5/15/27	58.6	13	10	95	10.8	0.37
A. N.	U	7/31/29	18	8/ 6/29	70.0	6 days	20	117	8.0	0.51
C. N.	C	11/18/27	29	8/ 7/28	59.2	9	30	89	14.0	0.50
J. O'C.	C	7/ 5/28	26	9/ 8/28	....	2	30	..	....	....
				10/29/28	51.2	3	20	76	....	....
J. O'H.	U	9/ 3/27	35	3/27/28	55.9	6	10	..	....	....
H. O.	H	12/12/28	23	3/ 6/29	78.2	3	10	..	13.3	0.45
E. O.	H	11/ 5/26	28	7/—/27	....	8	20	105	8.5	0.35
				11/ 7/27	....	12	30	95	....	....
J. P.	S	2/18/25	31	7/16/29	62.0	52	30	105	13.0	0.44
H. P.	U	12/27/28	33	1/ 8/29	44.0	12 days	30	82	9.1	0.36
L. P.	H	9/20/15	38	3/27/29	64.4	41	20	88	....	....
A. P.	H	6/16/19	26	7/22/29	41.7	121	20	91	14.1	0.41
H. P.	U	8/20/18	41	7/ 7/29	55.2	130	20	94	8.2	0.41
W. P.	U	4/30/27	44	6/11/29	83.0	26	20	124	12.2	0.42
E. P.	H	12/25/27	22	1/22/29	54.8	13	20	90	9.8	0.48
				4/16/29	54.4	16	20	..	....	....
				5/17/29	50.2	17	20	96	18.7	0.49
A. P.	U	6/29/29	25	7/ 9/29	47.4	10 days	20	90	8.4	0.40
				9/23/29	47.1	2	30	98	....	....
D. P.	P	8/ 4/27	30	3/20/28	65.2	7	30	92	10.1	0.49
				7/ 7/28	64.0	11	20	77	15.2	0.52
F. P.	P	8/31/24	33	6/25/29	54.2	57	10	100	12.0	0.49
				9/24/29	54.0	60	20	118	10.6	0.46
A. B. R.	U	7/25/29	26	7/31/29	75.2	6 days	20	122	....	....
				9/ 4/29	74.8	2	20	108	....	....
C. R.	P	10/20/26	36	3/20/28	55.6	17	30	90	12.6	0.48
D. R.	C	8/13/24	24	9/—/27	44.2	56	30	114	....	....
A. R.	C	3/26/23	22	5/25/28	57.2	61	30	105	10.2	0.39
P. R.	S	4/11/24	50	1/17/28	49.2	45	20	...	....	....
				3/21/28	49.6	47	30	84	....	....
C. S.	H	2/ 9/24	41	11/14/27	59.0	45	20	87	9.4	0.42
A. S.	U	11/15/28	26	1/ 8/29	52.0	2	40	...	....	....
H. S.	S	4/ 5/27	29	9/ 1/27	62.8	5	20	87	10.9	0.43
				11/21/27	63.2	7	20	77	12.6	0.45
				3/13/28	66.3	10	20	77	14.0	0.53
W. S.	U	5/16/28	35	7/24/29	62.3	14	20	91	....	....
J. S.	C	7/ 7/29	27	7/29/29	63.4	22 days	30	87	10.6	0.48

* C, H, P, S and U indicate catatonic, hebephrenic, paranoid, simple and unclassified types, respectively.

TABLE 1.—*Primary Data—Continued*

Name	Diagnosis*	Date Admitted	Age at Test, Years	Date of Test	Weight at Test, Kg.	Period in Hospital, Months	Test Positive, Gm.	Blood Sugar, Mg. per 100 Cc.	Total Nitrogen, Gm.	Creatinine Nitrogen, Gm.
A. S.	C	5/27/28	20	7/ 7/28	64.0	1	30	80	9.2	0.42
D. S.	C	11/30/28	24	12/12/28	67.4	12 days	30	108	11.5	0.50
				2/13/29	72.2	3	20	91	12.2	0.54
A. S.	H	12/17/13	52	7/ 9/29	....	187	20	97	10.0	0.52
				9/23/29	62.0	188	40	102	12.8	0.43
D. S.	H	1/31/28	34	6/ 5/28	56.4	5	30	111	9.1	0.40
G. S.	U	4/18/25	27	9/—/27	45.8	28	20	95	....	....
C. S.	P	5/ 5/27	38	3/13/28	59.5	10	20	87	12.4	0.49
F. S.	C	11/24/24	34	5/10/28	69.8	41	30	95	10.5	0.46
A. S.	C	5/ 3/28	23	5/29/28	54.1	25 days	10	108	....	....
G. S.	H	10/ 1/18	54	5/25/28	59.4	115	30	118	9.1	0.38
J. S.	S	4/ 5/28	26	7/ 3/29	64.2	15	30	100	9.4	0.45
				10/ 9/29	73.4	18	20	...	....	....
J. S.	U	6/27/27	38	4/16/28	61.6	10	20	...	13.1	0.47
A. T.	S	12/18/23	26	6/25/29	65.4	66	30	90	7.7	0.45
A. T.	H	8/22/24	34	6/26/29	56.1	58	20	83	....	....
W. T.	P	5/24/27	34	9/—/27	62.2	4	20	100	....	....
				8/15/28	64.2	11	20	101	....	....
				1/ 9/29	59.2	16	40	98	10.4	0.41
J. T.	P	6/ 6/24	30	9/—/27	54.2	39	20	85	10.7	0.46
				11/ 7/27	53.4	41	30	87	10.6	0.41
C. T.	C	4/ 1/27	20	5/15/27	56.6	1	30	83	....	....
E. U.	C	12/31/27	24	5/25/28	....	5	30	93	....	....
				8/20/28	62.6	8	30	85	....	....
H. VB.	H	3/21/28	33	12/20/28	51.6	9	30	124	9.5	0.40
A. W.	C	8/19/27	29	7/31/29	60.6	23	20	88	8.8	0.41
S. W.	C	7/16/23	39	6/19/29	....	71	20	117	8.3	0.39
				10/ 8/29	62.2	75	40	98	....	....
P. Y.	C	7/30/18	33	7/ 9/29	51.3	132	20	97	11.6	0.40
				10/ 9/29	61.3	135	10	91	10.2	0.44
H. Y.	U	5/16/29	63	6/ 6/29	64.0	21 days	30	111	8.8	0.37
A. Z.	H	12/19/19	41	7/ 9/29	62.2	276	40	88	8.4	0.38
L. Z.	U	12/19/19	42	4/16/28	53.0	100	40	69	6.4	0.36

* C, H, P, S and U indicate catatonic, hebephrenic, paranoid, simple and unclassified types, respectively.

tion is tabulated separately, irrespective of whether one or more tests were made on a given person. The heavy line gives the distribution as actually determined, while the broken line is a smoothed curve obtained by plotting the averages of each three contiguous points. The mode of the curve falls between 20 and 30, somewhere in the neighborhood of 25 Gm. The mode determined by Rowe [20] for adult male patients was 30 Gm. So far as one is justified in generalizing from one hundred and thirty-five cases, it appears that dementia praecox is characterized by an average depression of the galactose threshold amounting to approximately 15 per cent. This depression is of a similar magnitude to that of the basal metabolism depression as determined in eighty of the patients included in this study.[21]

The Relation of Weight to Galactose Tolerance.—In one hundred and eighteen cases we have records of the weights of the patients at the time the galactose tolerance was determined. In table 2, the average weight of all patients showing tolerances of 10, 20, 30 and 40 Gm., respectively, is recorded. These averages were closely similar in the four groups, ranging from 57.6 to 59.5 Kg. There is no consistent trend of weight difference with threshold difference to be brought out in this

21. Hoskins, R. G., and Sleeper, F. H: Basal Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **21**:887 (April) 1929.

way, though detailed statistical analysis in a large group might bring out a minor trend. The results bear out the conclusion of Rowe that the galactose threshold is independent of weight.

The Relation of Age to Galactose Tolerance.—Table 3 similarly indicates a complete lack of correspondence between age and tolerance. The average ages in the four groups vary only from 29 to 32 years and, in a series of this magnitude, are therefore statistically identical. Moreover, such differences as are shown are not consistently distributed.

The Relation of Period of Detention to Galactose Tolerance.—In view of the fact that, at best, detention in a hospital for mental diseases imposes various deviations from a normal method of living, there is considerable inherent probability that in the course of time this peculiar

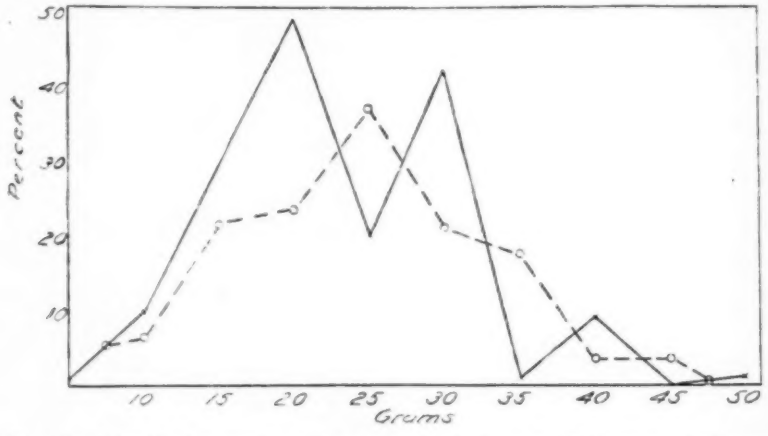

Fig. 2.—Distribution curves of galactose tolerance in 135 cases of dementia praecox. This is based on the total number of determinations, whether single or multiple, in each patient. The preponderance of the incidence of multiples of 10 is due to the fact that single determinations predominate and that these are made in gradations of 10 Gm. The solid line shows the actual distribution. The broken line is a smoothed curve obtained by averaging the numbers of each three contiguous points.

environment would be reflected in fundamental metabolic shifts. We have, accordingly, averaged by months the period of hospitalization in each of the four galactose tolerance groups (table 3). Since the period of hospitalization is highly variable throughout the series, a large number of cases would be required definitely to establish a trend. The average period ranged from twenty-one to forty-seven months in the various groups. The distribution is not consistent, but there is a suggestion of an inverse correlation between detention time and galactose tolerance. In the groups showing a tolerance of 30 or 40 Gm., the average period in the hospital is less than two years, while in the groups showing

tolerance of 10 and 20 Gm., the average period is more than three years. It is thought that more detailed statistical treatment should be deferred until a larger group of cases is available.

The Relation of Creatinine Output to Galactose Tolerance.—In dealing with samples of urine from psychotic patients there is ordinarily an element of uncertainty as to whether true twenty-four hour quantities are obtained. The bladder may not be completely emptied before the collection begins or at the end of the collection period. For two reasons it is not practicable to forestall this difficulty by catheterizing the patients: the demands on the time of the ward physicians would be inordinate, and the psychologic effect on the patients is often unfavorable

TABLE 2.—*Body Weight and Galactose Tolerance*

Tolerance, Gm.	Average Weight	Number of Cases
10	57.6	10
20	58.5	50
30	59.5	49
40	58.3	9

TABLE 3.—*Average Age and Period of Hospitalization, and Galactose Tolerance*

Tolerance, Gm.	Age, Years	Months of Hospitalization	Number of Cases
10	30	28	12
20	32	47	64
30	30	21	47
40	29	25	9

TABLE 4.—*Creatinine Nitrogen and Galactose Tolerance*

Tolerance, Gm.	Creatinine Nitrogen, Gm.	Number of Cases
10	0.41	10
20	0.44	56
30	0.45	50
40	0.42	9

when this or other unpleasant or terrifying procedures are included in the routine. For this reason, special importance attaches to the creatinine nitrogen determinations. As is well known, the creatinine output is largely independent of environmental and dietary vicissitudes. In table 4 is tabulated the average daily creatinine nitrogen output in each of the tolerance groups. In deriving this table, all cases were deleted in which the creatinine nitrogen figures fell outside the arbitrary limits of 0.35 and 0.55 Gm. The averages of these quantities in the various tolerance groups ranged from 0.41 to 0.45 Gm. The differences were of slight if any significance statistically, and they were not consistently distributed to indicate any significant correlation between galactose tolerance and creatinine output.

The Relation of Protein Consumption to Galactose Tolerance.—The cases selected on the basis of creatinine nitrogen output included in table 4 serve as the basis for table 5. The average total urinary nitrogen output in the various tolerance groups ranged from 10.0 to 10.4 Gm., a maximum variation of only 4 per cent. As in the case of the creatinine output, the differences of the total nitrogen output are so slight that no statistical significance can be attached to them in relation to the galactose tolerance.

Fasting Blood Sugar and Galactose Tolerance.—One hundred and sixty-nine fasting blood sugar determinations were made. The results are shown in table 6. It will be noted that the average blood sugar in the 10 Gm. galactose tolerance group was 93.7 mg. per hundred cubic centimeters of blood. In the other three groups of 20, 30 and 40 Gm., the average blood sugar was 96.1, 97.5 and 95.3 mg., respectively. The number of determinations in the 10 and 40 Gm. groupings were hardly numerous enough to be statistically valid, and it is quite possible that with a larger number of determinations these groups might approach those in the 20 and 30 Gm. groupings. The differences in the average

TABLE 5.—*Total Nitrogen and Galactose Tolerance*

Tolerance, Gm.	Total Nitrogen, Gm.	Number of Cases
10	10.0	10
20	10.2	56
30	10.4	49
40	10.1	9

TABLE 6.—*Fasting Blood Sugar and Galactose Tolerance*

Galactose Tolerance, Gm.	Average Blood Sugar, Mg. per 100 Cc. of Blood	Number of Determinations
10	93.7	11
20	96.1	81
30	97.5	64
40	95.3	13

TABLE 7.—*Percentile Distribution of Schizophrenic Types in Different Tolerance Groups*

	Types										
	Catatonic		Hebephrenic		Paranoid		Simple		Unclassified		
Tolerance, Gm.	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	Total Number Cases
10	2	8.0	4	11.8	1	4.6	1	7.2	4	10.8	12
20	6	24.0	20	58.8	12	54.5	7	50.0	19	51.4	64
30	16	64.0	8	23.6	9	40.9	5	35.6	9	24.3	47
40	1	4.0	2	5.8	0	0.0	1	7.2	5	13.5	9
Total	25		34		22		14		37		132

blood sugar in the four groupings were so slight as to indicate the absence of any significant correlation between initial blood sugar curves and galactose tolerance. The majority of the observations on blood sugar were well within the generally accepted normal range.

Percentile Distribution of Schizophrenic Types in the Different Tolerance Groups.—This distribution is recorded in table 7 and graphically in figure 3. It will be noted that the catatonic group shows the highest incidence of normal tolerance, 64 per cent of the patients having a tolerance of 30 Gm.; 32 per cent showed a lowered tolerance, and 4 per cent an increased tolerance. The hebephrenic group showed the highest incidence of lowered tolerance—70.6 per cent; 23.6 per cent had a

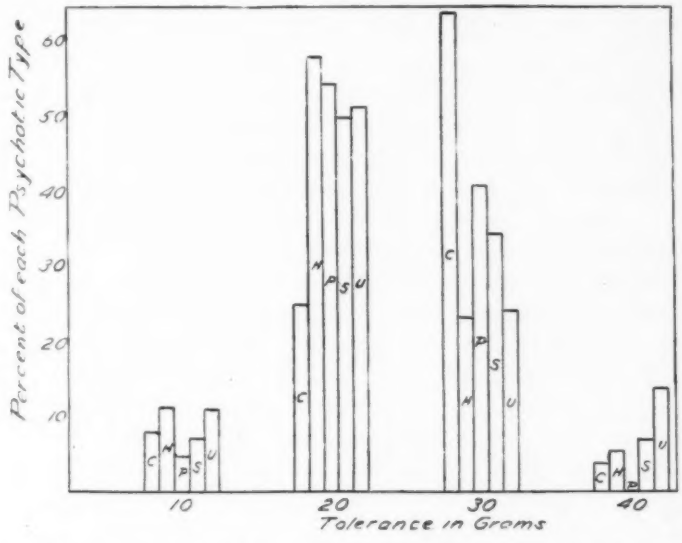

Fig. 3.—Percentile distribution of psychiatric types in each of four groups showing tolerances of 10, 20, 30 and 40 Gm., respectively. Note the relative uniformity of the distribution of all except the catatonic subjects. These strikingly predominate in the group having 30 Gm., i. e., normal tolerance. The initials stand for catatonic, hebephrenic, paranoid, simple and unclassified types respectively.

normal tolerance and 5.6 per cent an increased tolerance. In the paranoid group, 59.1 per cent had a lowered tolerance and 40.9 per cent a normal tolerance. In the simple group, 57.2 per cent had lowered tolerance, 35.6 per cent normal tolerance and 7.2 per cent increased tolerance. In the unclassified group, 62.6 per cent showed lowered tolerance, 24.3 per cent normal tolerance and 13.5 per cent increased tolerance. In our series, the highest incidence of lowered tolerance occurred in the hebephrenic group and the highest incidence of normal

tolerance in the catatonic group. This is definitely of interest, as the catatonic type has generally the best prognosis clinically.

COMMENT

As previously stated, in the relatively small number of cases in which multiple determinations were available, the same general variability was found in the galactose tolerance that has been reported by other observers in the blood sugar curves. This fact obviously means that determinations on a few patients can afford no basis for deductions. Only with the accumulation of enough cases so that one may be reasonably sure that incidental deviations in one direction will be compensated by those in another, can valid averages be determined and conclusions drawn. At the present stage of our studies, we feel disposed only to point out trends. Ultimately, it is hoped that a sufficiently large body of data will be secured to justify detailed statistical analysis. Within the limitations suggested, our data indicate a systematic depression of galactose tolerance as characteristic of dementia praecox. This adds one more item to the growing list indicating generalized depression of those bodily activities that are especially susceptible to endocrine or autonomic nervous influences. The fact that the depression was most marked in the hebephrenic and least in the catatonic group adds weight to the assumption that such depression is a valid characteristic of the psychosis.

One of the potentially important sources of error in the galactose tolerance test is the occurrence of liver dysfunction. We were early led to suspect a significant increase in liver involvement in dementia praecox, and for several months included routine studies of the van den Bergh reactions, bromsulphthalein output and Graham tests, together with "urobilinogen" determinations in the urine. This phase of the work has not yet reached a finally conclusive stage, but our present impression is that liver dysfunction is not an important factor.

Rowe [20] showed that lesions of the brain and spinal cord, malignant neoplasms, syphilis, pernicious anemia, hypertension, psychoneuroses, asthma (in patients to whom epinephrine has been given) and diseases of the liver all tend to depress the tolerance. In our series, Wassermann tests were negative in all patients; there were no focal symptoms of lesions in the brain or cord; no patients had hypertension or asthma, and there were no cases of primary anemia. Work has been reported on the effects of arthritis and tuberculosis on the carbohydrate metabolism. None of our patients had arthritis. Several of the patients showed evidences of arrested tuberculosis, but in these cases at the time of study no symptoms of the disease were present, and it is doubtful that the tuberculous process per se had any effect on the carbohydrate metabolism. Various patients gave evidence of endocrine involvement.

Some of these cases have been reported,[22] and others will be the subject of later discussion.

SUMMARY AND CONCLUSIONS

1. The galactose tolerance was determined one or more times in one hundred and thirty-five cases of dementia praecox.

2. The tolerance level was constant in fifteen and variable in twenty-four of the thirty-nine cases in which multiple determinations were made. Similar variability has been noted by others in the blood sugar curves following the ingestion of dextrose.

3. In the series as a whole there was a downward trend of the galactose tolerance, averaging approximately 15 per cent. In 8 per cent of the subjects, the tolerance was above normal, and in 58 per cent it was below normal.

4. The catatonic group showed the highest incidence of normal tolerance and the lowest incidence of depressed tolerance. The hebephrenic group showed the lowest incidence of normal tolerance and the highest incidence of lowered tolerance. The galactose tolerance test appears to have some value in the differential diagnosis of the two types.

5. No relationship between weight, age, creatinine output, protein catabolism or initial blood sugar level and galactose tolerance could be detected. There was some evidence of a decrease of tolerance with the increase of the period of hospitalization.

6. A tendency to lowered tolerance for galactose is added to the list of characteristics of dementia praecox that indicate a depression of functions under endocrine or autonomic control.

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22. Hoskins and Sleeper: Endocrinology **13**:245 (May and June) 1929.

THE ARGYLL ROBERTSON PHENOMENON*

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The definition of the Argyll Robertson pupil is usually given as a condition in which the pupil does not respond to light but does respond in accommodation and convergence. There are those who hold that the light reflex must be entirely abolished and who do not recognize this phenomenon if any light reaction is preserved. While this may conform to the conception attributed to Argyll Robertson, it is a source of error. It must be assumed that the loss of the light reflex has been complete from the beginning, and this would imply an abrupt onset of the symptoms. In this method of reasoning, all preliminary stages to the production of an Argyll Robertson pupil are ignored. It is sometimes stated in an ophthalmologic report that the pupil does not respond to light, but does respond in accommodation and convergence without any reference to the manner in which the light response is tested. An abortive Argyll Robertson pupil has much the same clinical value as the completely developed phenomenon which is generally recognized as the Argyll Robertson pupil; by the method of reasoning to which allusion has been made, the value of the preliminary stage is ignored. It would be possible to drop the name of Argyll Robertson and to speak of the phenomenon as reflex rigidity to light, and yet it seems desirable to retain the name of one who has made a brilliant clinical discovery, and to speak of the preliminary stage as an abortive Argyll Robertson reflex.

In all four cases that Argyll Robertson described in his paper on this subject,[1] the pupils were "insensible to the influence of light." He emphasized the myosis in all four cases, and of his fourth case he said: "Although it is certainly not a typical example, I here include it, because the myosis was well marked." Those who insist that the Argyll Robertson pupil implies complete inaction to light are likely to forget that Argyll Robertson regarded myosis as essential in the phenomenon that he described.

In his four cases the symptoms indicated advanced disease of the nervous system. Even in the fourth case the disease cannot be considered as incipient. Involuntary jerking of the lower limbs, impaired micturition, ataxic gait and pronounced Argyll Robertson pupils are definite signs of disease.

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* Submitted for publication, June 16, 1930.

* Read at a meeting of the Philadelphia Neurological Society, May 23, 1930.

1. Robertson, Argyll: Four Cases of Spinal Myosis; with Remarks on the Action of Light on the Pupil, Edinburgh M. J. **15**:487, 1869.

In describing the Argyll Robertson pupil as the complete loss of light reflex, often no mention is made of the fact that the optic nerve on one or both sides shows marked choking and impaired vision and, even more important, atrophy. It is true that with these observations a light reflex may often be obtained, as the so-called "pupillary fibers" of Gudden are often more resistant than the visual fibers, but there comes a time in every case of atrophy of the optic nerve, if it is progressive, when the "pupillary fibers" also become affected and their control is weakened or abolished. If only weakened, the light reflex is impaired but not lost. It is conceivable, when optic atrophy is present and an Argyll Robertson pupil is observed, that a false interpretation may be made and the phenomenon attributed to a gross lesion in the terminal portion of the tract of the "pupillary fibers" in the region of the corpora quadrigemina, whereas it is quite as likely that these fibers have been damaged either in the optic nerve or the optic tract. In such a condition as this a false localization may be made.

When the examiner states that the reaction to light is abolished, if he is accurate, he must also state what has been his method of examination. It has been known for many years that a pupil may respond to one form of light and not to another, and that the response is not always the same to daylight as to electric light. It is also true that the response depends on the degree of illumination of the eye and is greater under a strong electric light than it is under a weak one, and again, that a pupil that has been in the dark and therefore resting may give a light response when first tested, but not later. Under these varying conditions, the strict definition mentioned previously becomes of questionable value.

It is uncertain whether the Westphal-Edinger nuclei belong to the oculomotor nuclei or not. Cassirer and Schiff, Bach and Neiding, and others do not accept it as such, whereas Bernheimer, Ruge and others do. It is even disputed whether the various muscles innervated by the oculomotor nerve are represented in distinct nuclei or not. Most investigators support Gudden in the opinion that "pupillary fibers" exist in the optic nerve and undergo partial decussation in the chiasm.

REPORT OF A CASE

A patient whom I examined apparently had tabes; her husband had syphilis. She showed loss of patellar and achilles tendon reflexes, the Romberg sign, incoordinate gait, pains throughout the body which did not seem to be of the sharp shooting character and tabetic ocular signs. The interesting feature of the case was in the ocular observations. The left pupil varied in size while under observation. At one moment it was large and a little later, small. In taking the light reflex on several occasions, I found that when I first illuminated the left pupil it dilated slightly, i. e., that the patient had the paradoxic pupillary reflex

to light. This was not always present, and was more likely to be found at the first examination. The left pupil did not contract in the slightest degree in direct or consensual light reflex. It contracted promptly in convergence, but after convergence had ceased the dilatation of the left pupil was exceedingly slow, whereas that of the right pupil was normally prompt. Visual acuity was normal in each eye: 5/5. There was no involvement of the left iris by synechiae in such a way as to bind it down, as might occur from a former iritis. Dr. Fry found no evidence of such a lesion of the iris, and the fact that the left pupil contracted promptly in convergence showed that there was no mechanical disturbance in the iris itself. The action of the right pupil was normal. It is important that the right pupil contracted promptly not only to direct, but equally so to consensual, light reflex.

COMMENT

It is certain that light impulses from the left eye in some way reached the pupillary center in the right oculomotor nucleus. As there was no evidence of optic atrophy in either eye and no involvement of the iris, and as there was an open pathway for afferent light impulses from the left eye to the right pupillary center, it is difficult to imagine that the condition of the left pupil could in any way depend on a lesion of the visual pathways. The lesion was apparently in the center of pupillary innervation of the left eye in the oculomotor nucleus. The case is clinical proof that there must be a center in the oculomotor nucleus of each side that is concerned with the function of pupillary action on the same side. Such a center is supposed to be the Westphal-Edinger nucleus. Winkler stated that there is no case on record in which the Westphal-Edinger nucleus has been totally destroyed and pupillary reactions have been preserved, but he stated that there are cases on record in which there has been partial destruction of this nucleus and pupillary reaction to light has been preserved. The case that I have described may be one of complete destruction of the left Westphal-Edinger nucleus, and although it is only a clinical case and lacks anatomic proof, it is important in offering a strong suggestion as to the existence of a center concerned in pupillary innervation. Cases like this are known in the literature as unilateral rigid pupil to light or unilateral Argyll Robertson pupil. They are not common but are well known.

The contraction of the left pupil in convergence is not a reflex action but is an associated movement and therefore in no way complicates the observations mentioned. Frequently no attempt is made in testing to separate the accommodation reaction of the pupil from that obtained in convergence.

The object of this brief communication is to call attention to certain fallacies in testing for the Argyll Robertson pupil which I have encountered in neurologic practice; for a more exhaustive study of this form

of pupil I must refer the reader to the excellent chapter by Kinnier Wilson in his book, "Modern Problems in Neurology."[2] Wilson has made it probable that a tumor in the vicinity of the third ventricle, aqueduct or anterior corpora quadrigemina may cause the Argyll Robertson pupil. It is important to note in the three cases that he reported that impairment of vision was stated to have been absent or slight.

2. Wilson, Kinnier: Modern Problems in Neurology, London, Edward Arnold & Company, 1928.

Clinical Notes

VOCAL MYASTHENIA OF POSTENCEPHALITIC ORIGIN

Report of a Case *

D. M. Olkon, M.D., Chicago

In 1878, Erb [1] described a form of bulbar paralysis with ptosis and weakness of the muscles of the jaws and neck, with atrophy and diminution of the electrical excitability which he called asthenic bulbar paralysis. In 1887, Oppenheim [2] described a similar form and stated that no particular microscopic changes were found by him or by Jolly who studied the tissues microscopically. He spoke of this condition as a progressive fatal neurosis with glossopharyngolabial paralysis without atrophy. Wilks, Eisenlohr, Karplus, Hoppe and others reported similar cases with marked dysarthria, dysphagia, weakness of the muscles of the tongue, palate and jaws, and fatigue of the trunk muscles. Goldflam,[3] in 1893, also described a similar form of bulbar paralysis, and stated that ptosis was a constant symptom, with fatigability of the muscles of mastication and deglutition and with bulbar speech. Many more such cases were reported later by Jolly, Strümpell, Oppenheim, Curschman, Hedinger,[4] Buzzard [5] and Steinert,[6] but in no instance was the etiology learned.

REPORT OF CASE

Clinical History.—A youth, aged 19, who was well developed and well nourished, was in good health up to the beginning of the present illness. Nine months previous to this report, the mouth began to fill with saliva; this condition grew worse progressively until it became of great discomfort; saliva was drooling out of the mouth. The condition still persists. Six months before examination, speech began to be nasal and the spoken words indistinct; this gradually grew worse, until it was difficult to understand him at times. Under close questioning, the patient related that three years previously he had a spell of drowsiness which had persisted for several weeks. He would become drowsy while riding on a

* Submitted for publication, March, 1930.

* Read at a Meeting of the Chicago Neurological Society, Jan. 16, 1930.

* From the Divisions of Neurology and Psychiatry, University of Illinois College of Medicine.

1. Erb, W. H.: Asthenische Bulbarparalyse, einen wenig bekannten Symptom, cited by Oppenheim, footnote 2.

2. Oppenheim, H.: Die myasthenische Paralyse, Handbuch der pathologische Anatomie der Nervenheilkund, Berlin, S. Karger, 1901.

3. Goldflam, S.: Ueber bulbärparalytischen Symptom Complex, Deutsche Ztschr. f. Nervenh. **4**:312, 1893.

4. Curschman and Hedinger: Deutsches Arch. f. klin. Med. **85**:578, 1905.

5. Buzzard, E. F.: Brain **28**:438, 1905.

6. Steinert: Deutsches Arch. f. klin. Med. **78**:346, 1905.

street car in the morning, was drowsy at his work and was always looking for an opportunity to doze. At this time he had his tonsils removed; the drowsiness disappeared, and he again felt well.

Examination.—The following observations were outstanding: (1) Marked sialorrhea, with drooling of saliva when talking. (2) Marked hyperhidrosis. While the patient was being examined, water actually trickled in drops from

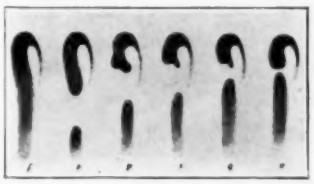

Fig. 1.—Archicapillaries greatly dilated, half empty and atonic. (After F. Müeller.)

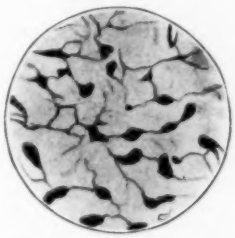

Fig. 2.—Capillaries with diverticulum-like formations. Small capillaries obliterated. (After F. Müeller.)

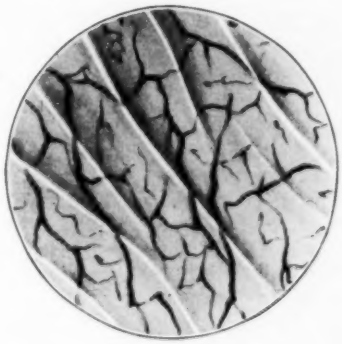

Fig. 3.—Extreme contraction of the smaller capillaries with atony and dilation of the larger capillaries. (After F. Müeller.)

under the arm pits, and the whole body felt as if it had been sponged with water. (3) Livid, diffuse and persistent dermographia. (4) Coarse tremor of the tongue. (5) Speech indistinct, nasal and bulbar in type, with a tendency to partial dislocation of the jaw, probably due to loss of tone in the masseter, temporal and pterygoid muscles. In the morning the speech was somewhat clearer, but it became less distinct as the day progressed. (6) Pronounced vasomotor and sympathetic disturbances.

Notwithstanding the apparent bulbar paralysis type of speech, there was no paralysis of the labial, palatal, lingual or pharyngeal muscles; there was no true dysarthria or aphonia. No atrophy of any muscles and no reaction of degeneration to electrical stimulation was present. There was no involvement of the cranial nerves. The deformity of speech seemed to have a character of its own.

All reflexes were present and normal; there were no abnormal reflexes; the abdominal reflexes were sluggish, and the Aschner phenomenon was pronounced. He had no weakness or rigidity in any other muscles of the body and there were no sensory disturbances. The eyegrounds were normal, and there was no visual field disturbance as to color or form. There was no involvement of the eye muscles. Serologic studies of the blood and spinal fluid gave negative results.

Capillary microscopy showed severe angiospasm (fig. 1). The archicapillaries were greatly dilated, half empty and atonic. There was a protracted pause in the filling of the microscopic vessels after contraction, and the dilatation that followed left the capillaries widely dilated, resembling flattened arches with a break near the top. The spasm phase is best represented in figure 2, where many diverticulum-like formations, due to the undue contraction, are seen and where the small capillaries have been obliterated. Figure 3 shows both extreme contraction and the resulting atony of the larger capillaries.

Diagnosis.—The condition reported points to a massive involvement of the brain, perhaps of the striatum, substantia nigra, etc.; it doubtless is a vocal myasthenia of postencephalitic origin, with a particular tonal asynergia and profound vasomotor and sympathetic imbalance. At first glance the case resembles the "asthenic bulbar paralysis" of Erb; but it differs markedly from such cases in the absence of paralysis in the muscles of speech, of atrophy and of involvement of the cranial nerves.

The parkinsonism, shown in the coarse tremor of the tongue, the sialorrhea, the pronounced Aschner and vasomotor disturbances and asynergia of the vocal muscles, distinguish this case as an outstanding symptom-complex from the "asthenic bulbar paralysis" type, and adds it to the many mimicries of the syndrome of epidemic encephalitis.

COMMENT

The patient, a male, aged 19, was well until nine months before presentation, when an increased amount and drooling of saliva made him very uncomfortable; it still persists. Six months before examination, speech became indistinct and nasal. In conversation the last sentences could hardly be understood, not because of faulty articulation, but because of the peculiar tonal mixup. When the patient was questioned, it was found that three years before he had had a spell of unusual drowsiness during work or play, which persisted for a few weeks, but that he gradually returned to his normal health.

Physical examination revealed marked sialorrhea, and hyperidrosis of a type that made the patient's entire body feel as though it were sponged with water. There was a persistent livid dermographia and a marked Aschner phenomenon. There was a coarse tremor of the tongue. The speech was indistinct, as if the nasal cavities and the pharynx were packed with some sort of loose packing. The lower jaw had a tendency to easy dislocation, and there was pronounced vasomotor atony of the surface blood vessels.

Notwithstanding the apparent bulbar type of speech, there was no paralysis of the labial, palatal, lingual or pharyngeal muscles, no true dysarthria and no reaction of degeneration of the muscles of the face, neck or mouth. The vocal cords were in close apposition, and the pharyngeal reflex was present. The cranial nerves were intact. All reflexes were of good quality, and there was no patho-

logic reflex, except that the abdominals were sluggish. The patient had no rigidity of the limbs. The eye muscles, eyegrounds and visual fields were normal.

Serologic examination of the blood and spinal fluid gave negative results. The blood sugar was 90, the spinal fluid sugar, 50 per hundred cubic centimeters. Microscopic examination of the capillaries showed severe angiospasm with pronounced atony of the entire subpapillary plexus of the fields examined.

The sialorrhea, vasomotor atony, tremor of the tongue, hyperidrosis and Aschner sign, without paralysis of the muscle, pointed to a striatal involvement and the vocal atony to an involvement of the basal ganglia. My diagnosis, therefore, was of a latent encephalitis with a residual severe vocal myasthenia, mainly of phonation. This report added one more case to the many serious complications of the disease.

SPECIAL ARTICLES

EPIDEMIC ENCEPHALITIS *

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During the past decade, the medical profession has witnessed with absorbing interest the appearance, development and spread of what is, to all intents, a new disease. Heralded from abroad by extensive reports and descriptions, there appeared in the cities of the Eastern seaboard in the autumn of 1920, examples of what seemed to those acquainted with neurologic disturbances to be an unfamiliar and remarkably interesting disease. One by one, the programs of the neurologic societies of the larger centers in the East recognized the advent of a clinical syndrome entitled "encephalitis lethargica." The presentation of patients, case reports, clinical and pathologic studies or etiologic investigations at almost every meeting devoted to medical or neurologic subjects indicated the widespread incidence of the disease and the interest which it aroused. The spread of the infection in ever widening circles during the winter was amply demonstrated by the appearance of similar reports from more and more distant localities, until it seemed as if the epidemic had penetrated into all parts of the United States, no matter how isolated.

EPIDEMIOLOGY

Statistics.—As is the case with all epidemics, it is difficult to obtain any definite idea of the extent of the inroads of this disease into the public health. Such figures as are available at the present time are not only grossly inadequate but actually misleading. The most ambitious

* Submitted for publication, Dec. 17, 1929.
* Read before the Clinical Research Society of New York, Jan. 2, 1930.

statistical study so far attempted is being carried on at the present time under the auspices of the William J. Matheson Survey of Epidemic Encephalitis. These figures deal with the cases actually diagnosed and reported in fourteen countries and are unfortunately incomplete on account of the fact that, as will be amplified later, only a small proportion of the total morbidity receives official cognizance. A much more serious deficiency arises, however, from the fact that many countries in which, from the literature, it is well known that extremely widespread disseminations of the disease took place, are entirely absent from the statistical calculations, no figures being reported as to morbidity or mortality. Such is the case with both France and Germany, in which countries the local medical profession contributed voluminously to the literature of the disease while their boards of health or similar agencies have remained silent in regard to any official statistical contribution. Spain also, the country which gave its name to the disease, Spanish influenza, with which epidemic encephalitis seemed so closely interwoven, reported no official figures. It is well known that only a fraction of the cases that occurred have been reported. It is idle to speculate what this proportion is, but certainly it would not be far beside the point to estimate that probably not more than 25 per cent of the cases were reported. The figures as gathered by the Matheson Survey throw a great deal of light on the varying pandemicity and mortality of this plague during the years from 1919 to 1927. During these years, 42,998 cases of encephalitis were reported. This total, assuming that it represents only one fourth of the actual cases which occurred, would place the morbidity in countries where the disease was reportable at about 176,000. When to this total are added the countries that have reported no figures, such as France, Germany, Spain, China, Japan, India, etc., the total is swelled to unbelievable proportions. The vast extent of this inroad into the health of the world may be easily recognized from these probably very conservative estimates. The Matheson Survey also illustrates very well the varying fluctuations of the disease. In 1920, 7,739 cases were reported as occurring in fourteen countries; this number fell to 4,735 in 1921 and touched the epidemic bottom in 1922, when 1,468 cases were reported. In 1923, the number rose to 3,597 and in 1924, the fastigium of the epidemic was reached with 9,393 cases. This total decreased to 6,470 in 1925, 5,774 in 1926 and 3,832 in 1927. In 1928, up to July, twenty-four countries reported 1,847, which would indicate that the total number is still decreasing. The figures for New York City show a considerable agreement with the fragmentary world figures as already quoted. In 1919, before the recognition of this disease was well established, there were reported to the board of health 118 cases; in 1920, 573; in 1921, 528. In 1922, this number increased to 611 and in 1923

reached the upper limit of 923. From that time the figures have declined gradually to 232 for 1927. The unreliability of these figures as representative of the total morbidity may be gaged by the New York mortality incidence which has ranged from 29 per cent of the morbidity in 1919 to 69 per cent in 1927. This is certainly not the mortality rate which the close contact of neurologists with this disease would lead them to accept, and it strengthens the impression that only the severe cases of this disease are reported and that in all probability thousands of cases come under the attention of neurologists and internists which are not reported to the board of health.

Dissemination.—The epidemic character of the disease has now disappeared, and in its place an endemic contagion has established itself characterized by ever recurring new cases, while the enduring ravages of the disease are filling the consulting rooms of clinics and hospitals with the sequelae and the more chronic forms of this incapacitating infection. Scarcely a day passes in any of the large neurologic clinics in which is not seen at least one case of the late effects of this disease, and the wards of the hospitals for chronic invalids are crowded with the mutilated victims of this infection. On Dec. 30, 1928, three patients with the parkinsonian type applied for admission as new cases to the New York Neurological Institute Outpatient Department alone.

The itinerary of this disease is of great interest and, as has been the case with many of the scourges which have preceded it, its place of origin seems to have been laid in that "hot-bed and breeding place of epidemics," southeastern Europe [1] where it is contiguous to the Near East. The first authentic published reports in Vienna in 1917, described tributed by von Economo [2] who, writing in Vienna in 1917, described a disturbance characterized by lethargy, mental hebetude, masking of the facies and oculomotor disorders associated with other functional deviations indicative of widespead involvement of the central nervous system. Its relatively rapid progress is clearly manifested by the sequence of the reports of the disease which appeared in topographic order from Paris, in 1918, by Netter; [3] in the same year by Batten,[4]

1. Boyd, W.: Epidemic Encephalitis: A Study of Seventy-Five Cases with Sixteen Autopsies, Ann. Med. **1**:195, 1920-1921.

2. Von Economo, C.: Encephalitis lethargica, Wien. klin. Wchnschr **30**:581, 1917.

3. Netter, A.: L'encéphalite léthargique épidémique, Bull. Acad. de méd., Paris **79**:337, 1918; L'encéphalite léthargique épidémique, Paris méd. **8**:81, 1918; Existence de l'encéphalite léthargique en Angleterre, Bull. et mém. Soc. méd. d. hôp. de Paris **42**: 384, 1918.

4. Batten, F. E., and Still, G. F.: Epidemic Stupor in Children, Lancet **1**: 636, 1918.

Hall [5] and Wilson [6] in Great Britain and from Italy in 1918, by Re [7] and Ascoli.[8] The disease was transported across the Atlantic in 1919 and the dissemination in this country took place from east to west, radiating outward from the debarcation ports of New York, Boston, Philadelphia and southern cities until it was a stranger to no part of this land, reaching the Pacific coast in a relatively short time.

History.—As the symptom picture became more familiar and better understood, a search of the medical literature of the past soon demonstrated that this was not a new disease but only one to which attention has been dramatically directed by the enormous number of its victims. Careful investigation has resulted in the unearthing of reports of various kinds going back further and further into the archives of medical history, and a perusal of these descriptions has supplied a respectable perspective of this disease and provided it with an ancient lineage. In classic times, a similar syndrome was described by Aretaeus and Galen under the title of phrenites or causus. The Dark Ages, with their submergence of everything which even had the odor of science, is equally silent in regard to this scourge, but in the early years of the Renaissance can again be found descriptions exceedingly suggestive of this disease appearing from clinicians such as De Sousa in Lisbon, who wrote of mendorra or mordorillo in 1521, the pestilence soporeuse by Amatus in Italy in 1561, lethargy with ocular palsies by Albrecht from Germany in 1695, while Camerarius of Tübingen in 1718 described a disease under the title of Schlafkrankheit or Somnolence with Ophthalmoplegia.[9] In 1768, Lepecq de la Cloture recorded the appearance of a symptom picture which he called coma somnolentum, and Ozanam,[10] in 1835, reported cases of catarrhal fever associated with somnolence. In 1875, Gayet,[11] of Lyon, described a disease characterized by an ophthalmoplegia of subacute onset accompanied by apathy and somnolence. The last few years of the nineteenth century contributed rather extensive reports of an epidemic in Italy by Lon-

5. Hall, A. J.: Epidemic Encephalitis, Brit. M. J. **2**:461, 1918.

6. Wilson, S. A. K.: Epidemic Encephalitis, Lancet **2**:7, 1918.

7. Re, G.: La cosidetta encefalite letargica acuta epidemica considerata come una manifestazione nervosa dell'influenza, Riforma med. **35**:851, 1919.

8. Ascoli, V.: Sulla cosidetta encefalite letargica, Riforma med. **35**:945, 1919.

9. Tilney, F.: Epidemic Encephalitis. Practical lectures delivered under the auspices of the Medical Society of the County of Kings, 1923-1924, New York, Paul B. Hoeber, 1925, p. 400.

10. Ozanam, J. A. F.: Histoire médicale générale et particulière des maladies épidemiques, contagieuse et épizoötiques qui ont regnés en Europe depuis les temps les plus reculés . . . , ed. 2, Paris, 1835.

11. Gayet: Affection encéphalique (encéphalite diffuse probable), Arch. de physiol. norm. et path. **2**:341, 1875.

guet [12] under the title of nona or malattia de la nona, in 1892, and central nervous system complications in influenza by Pfuhl,[13] also in 1892. During the eleven years since the essential character of this disease became well established, a flood of communications has appeared, reaching a maximum in 1920 and 1921 and only slowly receding, while reports are still appearing which are particularly concerned with special features of this kaleidoscopic symptom-complex. In 1920, the Association for Research in Nervous and Mental Disease compiled a bibliography of the more important communications describing this disease and recorded about 400 articles. In 1928, the *Cumulative Index Medicus* catalogued almost 150 titles. Between the years 1921 and 1928, great numbers of contributions have appeared which have dealt with almost every conceivable phase of this subject. Despite these many studies, many aspects of the disease still remain obscure and a satisfactory classification of the major types of disturbance consequent on this infection is still much to be desired.

ETIOLOGY

The bacterial agent causing this widespread disease still remains to be proved. The remarkable association of this disease with the prevalence of epidemic influenza, which has been frequently noted, gave rise during the early years of acquaintance with this infection to the belief that it was a particular strain of influenza bacillus which, through special neurotropic characteristics, gave rise to a cerebral form of influenza. Although this view has been almost universally discarded, Patton,[14] as late as 1927, wrote of encephalitis lethargica as an influenza encephalitis. As, however, the special qualities of this disease became apparent and through the uniform failure to isolate from the central nervous system anything that even remotely resembled this bacterial agent, the assumption that the known influenza germ and the unknown encephalitic virus flourish in symbiosis became prevalent and gained a considerable degree of acceptance. This view is still rather widely held, its protagonists claiming that the influenza bacillus precedes the encephalitic infection and renders the central nervous system an easy prey to the symbiotic organism. Bassoe,[15] in considering eleven typical cases of encephalitis that had been under his observation,

12. Longuet, R.: La nona, Semaine méd. **12**:275, 1892.

13. Pfuhl, A.: Bacteriologisches Befund bei schweren Erkrankungen des Centralnervenssystems im Verlauf von Influenza, Berl. klin. Wchnschr. **29**:879 and 1009, 1892.

14. Patton, W. D.: Encephalitis Lethargica: Influenza Encephalitis, Canad. M. A. J. **17**:436, 1927.

15. Bassoe, P.: Epidemic Encephalitis (Nona), J. A. M. A. **72**:971 (April 5) 1919.

could find no definite disease preceding the onset of the encephalitis but was so impressed by the debilitated condition of his patients that he suggested that the virus becomes neurotropic only because of an increased susceptibility of the patient. On the other hand, many observers believe that the entire disease with not only its neural but also its systemic manifestations is but the result of only one infecting agent, thus bringing it into line with the accepted view of poliomyelitis, in which there is a period of general infection with its systemic evidences of invasion—the restlessness, malaise, gastro-intestinal symptoms, fever, etc.—which precede the more intimate and destructive characters of the disease, the latter making themselves manifest only in the second phase, that of neural invasion. It is well known that many patients fail to develop the complete cycle of poliomyelitis with its secondary neural involvement and are considered abortive cases. This may well be the case also with epidemic encephalitis, for many persons during the various recrudescences of this disease have manifested mild catarrhal and general infective evidences but have failed to develop any of the destructive neural involvements of either the acute or the chronic variety.

A great deal of conscientious, painstaking investigative effort has been expended in the attempt to isolate the specific organism, but no one has as yet been able to advance irreproachable evidence of the cultivation of any organism that can be held responsible according to the postulates of Koch for the causation of this disease. Many organisms have been described as its cause. In 1917, von Wiesner [16] described a gram-positive diplostreptococcus, which was said to have been isolated from one of Economo's cases, with which he inoculated apes intracerebrally and produced a hemorrhagic encephalitis; but he could not demonstrate the same pathologic picture which was found in patients dying of encephalitis. House,[17] in 1920, reported the isolation of a green-producing diplococcus from the brain of a patient dying of epidemic encephalitis which was not lethal for rabbits. He, however, described no pathologic changes in his rabbits, confining his observations to immunologic phenomena. Dunn and Heagey [18] reported the isolation of a green streptococcus from the blood of a patient who developed lethargy and diplopia. Certain immunologic studies were made but no pathologic investigations were carried out.

16. Von Wiesner, R. R.: Die Aetiologie der Encephalitis lethargica, Wien. klin. Wchnschr. **30**:933, 1917.

17. House, S. J.: Observations on a Green-Producing Coccus from the Brain in a Case of Encephalitis, J. A. M. A. **74**:884 (March 27) 1920.

18. Dunn, A. D., and Heagey, F. W.: Epidemic Encephalitis: Including a Review of 115 American Cases, Am. J. M. Sc. **160**:568, 1920.

Rosenow,[19] of the Mayo Clinic, has carried on and is still pursuing extensive studies on the bacteriology of this disease; he had contributed extensively to the literature on this subject. The great majority of his experiments have been carried on by culturing and subculturing nasal, nasopharyngeal, dental and tonsillar exudates from patients suffering from this disease, isolating pure strains of streptococci and injecting them in almost every known manner into laboratory animals, chiefly rabbits. He claims great specificity for the various strains of streptococci and staphylococci which he has isolated, stating that bacteria obtained from lethargic patients produced lethargic rabbits; that from maniacal patients produced maniacal rabbits; from myoclonic patients, myoclonic phenomena, and from choreiform patients, the same kind of rabbits. He also described the transmission of epidemic hiccup by means of the same technic and the production in rabbits of diaphragmatic spasms. He stated that typical and specific symptoms and lesions have been produced by these organisms. He has used these organisms with varying success in the production of antigens by injection into horses. He stated that most of the strains isolated are immunologically identical and closely related to the pleomorphic streptococcus which he isolated as the cause of poliomyelitis. He was not able to regain the infecting organism from the brains of his experimental animals.

In 1919, Loewe and Strauss,[20] working with filtrates from nasal and nasopharyngeal washings obtained from patients suffering from epidemic encephalitis, reported the isolation of a filtrable virus which they carried into the twelfth generation through successive inoculation and recovery from the brains of rabbits. Injection of this virus resulted in the production of typical microscopic pictures in the animals used.

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19. Rosenow, E. C.: Further Studies on the Etiology of Epidemic Hiccup (Singultus) and Its Relation to Encephalitis, Arch. Neurol. & Psychiat. **15**:712 (June) 1926; Localization in Animals of Streptococci from Cases of Epidemic Hiccup, Encephalitis, Spasmodic Torticollis and Chorea, ibid. **19**:424 (March) 1928; Diaphragmatic Spasms in Animals Produced with a Streptococcus from Epidemic Hiccup: Preliminary Report, J. A. M. A. **76**:1745 (June 18) 1921; Experimental Studies on the Etiology of Encephalitis: Report of Findings in One Case, ibid. **79**:443 (Aug. 5) 1922; Specific Serum Treatment of Epidemic (Lethargic) Encephalitis: Further Results, ibid. **80**:1583 (June 2) 1923. Helmholz, H. F., and Rosenow, E. C.: Three Cases of Acute Encephalitis Treated with Specific Serum, J. A. M. A. **79**:2068 (Dec. 16) 1922.

20. Loewe, L., and Strauss, I.: Experimental Studies in Encephalitis Lethargica, Proc. New York Path. Soc. **20**:18, 1920. Strauss, I.; Hirshfeld, S., and Loewe, L.: Studies in Epidemic Encephalitis (Encephalitis Lethargica): Preliminary Report, New York M. J. **109**:772, 1919. Loewe, L., and Strauss, I.: Etiology of Epidemic (Lethargic) Encephalitis: Preliminary Note, J. A. M. A. **73**: 1056 (Oct. 4) 1919.

Further studies and cultural investigations resulted in the identification of minute globular refractile bodies occurring singly, in diplo-forms, chains and clumps with which they carried out extensive bacteriologic and clinical investigations. These studies have never been confirmed, except by Thalhimer, who was associated with the former investigators. Neustaedter [21] emphasized the immunologic characters of the etiologic agent of epidemic encephalitis and claimed that poliomyelitis and this disease are possibly due to variations of the same causative factor.

Levaditi and Harvier [22] reported a series of experiments carried out on various laboratory animals in February, 1920, with the isolation of a filtrable virus which could be carried through a series of animals. McIntosh and Trumbull [23] reported that glyceride extracts from the brain of a patient dying of epidemic encephalitis caused identical disturbances in rabbits and that similar pathologic pictures were obtained. Similar reports have been recorded by Doerr, Schnabel and others. The results of these and many other experiments were fully reviewed by Flexner [24] in 1923, who stated that the results so far reported were so conflicting that no completely satisfying result could be obtained.

Evans and Freeman,[25] in 1926, succeeded in isolating a pleomorphic streptococcus which they found to be highly virulent when inoculated intracerebrally into rabbits. They had the opportunity of studying three cases, both clinically and after death, but succeeded in their experimental and cultural studies in only one of the three cases at their disposal. In their successful case they were able to obtain a virulent organism from nasal washings, from the heart blood and from emulsions made from the mesencephalon. This organism corresponded to the streptococcus obtained by von Wiesner, Rosenow and several others. The rabbits and monkeys into which injections were made presented symptoms which strikingly resembled the clinical manifestations of the disease in man. When injected intravenously, the organism showed an elective localization in the brain, there being no evidence of any inflam-

21. Neustaedter, M.; Hala, W. W., and Banzhaf, E. J.: A Further Contribution to the Study of Endemic Encephalitis in Its Relation to Poliomyelitis, New York State J. Med. **24**:1, 1924.

22. Levaditi, G., and Harvier, P.: Recherches expérimentales sur le virus de l'encéphalite léthargique (encéphalite épidémique), Bull. Acad. de méd., Paris **83**: 365, 1920.

23. McIntosh, J., and Trumbull, H. M.: The Experimental Transmission of Encephalitis Lethargica to a Monkey, Brit. J. Exper. Path. **1**:89, 1920.

24. Flexner, S.: Epidemic (Lethargic) Encephalitis and Allied Conditions, J. A. M. A. **81**:1688 and 1785 (Nov. 17 and 24) 1923.

25. Evans, A. C., and Freeman, W.: Studies on the Etiology of Epidemic Encephalitis, Pub. Health Rep. **41**:1095, 1926.

matory reaction in tissues other than those of the nervous system. The meninges were heavily infiltrated with leukocytes and lymphocytes, and showed a direct extension of the inflammatory process into the underlying brain substance. There appeared severe parenchymatous degenerative changes, a marked neuroglial reaction was present, and the perivascular lymph channels were heavily infiltrated. The most marked reactions were found in the mesencephalon and isolated hemorrhagic areas of inflammation were found in the basal ganglia of the experimental monkeys.

Greenfield [26] reviewed the literature of epidemic encephalitis extensively and from the reports of others and his own observations came to the conclusion that the disease is caused by a virus which no one has even seen or been able to cultivate on an artificial medium. After carefully reviewing the evidence, he concluded that many of the recent reports of the transmission of the disease to animals are invalid. He cast doubt on the acceptability of the evidence adduced by Loewe and Strauss and also that presented by Kling and others in Sweden.

Zinsser,[27] in a critical review, surveyed the epidemiologic, pathologic and bacteriologic data that have been accumulated in the numerous reports on these aspects of the disease. He quoted the report of Parsons,[28] Stallybrass,[29] Kling and Liljenquist,[30] Wilmer [31] and MacNalty [32] to establish definitely the contagious character of the disease. Zinsser discussed the reports of the transmissibility of the disease in considerable detail and concluded as follows: "If one assumes the possibility of a mutation of an organism into a filtrable virus form, and together with that, a modification in pathogenic properties during the course of the mutation, one could accept as a solution of the problem not only the work of Evans and Freeman, but that of others who have cultivated bacteria. It is still a far cry experimentally to such a premise, however, and logic forces one at the present time to reject the bacterial

26. Greenfield, J. G.: The Pathology of Epidemic Encephalitis, Brit. M. J. **2**:535, 1927.

27. Zinsser, H.: The Present State of Knowledge Regarding Epidemic Encephalitis, Arch. Path. **6**:271 (Aug.) 1928.

28. Parsons, A. C., and MacNalty, A. S.: Report on Encephalitis Lethargica, Great Britain, Ministry of Health. Reports on Public Health and Medical Subjects, 1922, no. 11.

29. Stallybrass, C. O.: Encephalitis Lethargica: Some Observations on a Recent Outbreak, Lancet **2**:922, 1923.

30. Kling, C., and Liljenquist, F.: Épidémiologie de l'encéphalite léthargique, Compt. rend. Soc. de biol. **84**:521, 1921.

31. Wilmer: Report of the Massachusetts Department of Health.

32. MacNalty, A. S.: Report on Outbreak of Encephalitis Lethargica in a Girls' Home, Great Britain, Ministry of Health. Annual Report of the Chief Medical Officer, 1919-1920, appendix vii, p. 357.

causation of this disease" on account of certain discrepancies, such as: (1) the difference in symptoms in animals preceding death from those of man and also from animals secondarily infected; (2) fundamental differences in pathology in man and experimental animals; (3) a different immunity in encephalitic, herpes and filtrable virus disease from that in streptococcus infections, and (4) the assumption of an interrelationship between the bacteria and a filtrable virus stage with its manifest attendant difficulties. He believed that the evidence at the time of an actual mutation is entirely too unreliable for acceptance and he came to the tentative assumption that the disease is due to a filtrable virus. Zinsser elaborated in considerable detail the present state of knowledge in regard to herpes and presented, in connection with this disease, a general discussion of the characteristics of the filtrable viruses. In considering the relationship between herpes and encephalitis, investigation has led a number of authors to believe that encephalitis is due to an increased development of neurotropism on the part of the herpetic virus. Zinsser stated that it is certain that the various strains of the herpes virus, whatever the locus of the original human vesicle, can be shown to be identical by cross-immunization. He expressed the belief that herpes as a disease is due to the activation of an agent latently present in the patient's body and rendered operative by a large number of activating factors, such as injury or inflammation of nerves, toxemia of disease, typhoid inoculation, etc. Doerr [33] and his colleagues have assumed an endogenous ubiquity with the frequent latent presence of the causative agent in widely scattered tissues. Doerr and Vöchting [34] noted that occasionally herpetic rabbits developed general symptoms referable to an involvement of the nervous system.

The virus of herpes can be transmitted through an unlimited series by intracerebral inoculations of brain substances preserved in glycerin and it can be preserved almost indefinitely in this medium, thus corresponding to similar phenomena demonstrable for the virus of poliomyelitis. Herpes virus has never been cultivated and cannot be demonstrated under the microscope, although a number of observers have found a nuclear inclusive body similar to those found in reactions produced by other filtrable viruses. Additional data discovered by immunologic experiments with herpes virus and other viruses are adduced to show their close relationship.

Zinsser further presented a list of instances in which strains of virus of any kind were definitely isolated from the central nervous system

33. Doerr, R.: Herpes und Encephalitis, Centralbl. f. Bakteriol. **97**:76, 1925-1926.

34. Doerr, R., and Vöchting, K.: Études sur le virus de l'herpes fébrile, Rev. gén. d'opht. **34**:409, 1920.

of encephalitic cases as reported by Levaditi and Harvier, Doerr and Schnabel, Doerr and Berger, Berger, Schnabel, Doerr and Zodansky, Luger and Landa and Perdran. Zinsser summed up the evidence as showing that the herpetic virus may develop neurotropism and produce an encephalitis in animals and that the virus has been recovered from the brain and spinal fluid in fatal cases of epidemic encephalitis in man. These facts would appear to compel the acceptance of an etiologic relationship were it not for a number of important difficulties. The occasional presence of herpes virus in the spinal fluid of persons who were not suffering from nor have had epidemic encephalitis has been proved incontrovertibly by certain observers, such as Flexner,[25] so that the virus discovered may be an accidental admixture having no relationship to the disease. Zinsser was unable to agree with Levaditi that the herpes virus in a somewhat altered condition represents the actual virus of epidemic encephalitis and agreed with Flexner that none of the virus strains so far isolated can be conclusively accepted as the cause of epidemic encephalitis. He then stated that he was strongly inclined to the opinion that the herpes virus and that of encephalitis are either identical in the sense of Levaditi or closely related. He did not indicate what the exact distinction is in regard to his disbelief and belief in Levaditi's conclusions. He maintained, however, that epidemic encephalitis is an infectious disease in which the virus produces changes comparable to those found in poliomyelitis and to some extent in rabies. He expressed the belief that there is a considerable analogy between herpes and encephalitis, that the virus of the former is widely prevalent in the tissues of man, that its neurotropism has been proved in animals, that the herpetic virus has been rarely but definitely demonstrated in man and that it may, in persons specially predisposed by debilitation or preceding provocative disease, acquire a neurotropism. He expressed the opinion that there can be little doubt that the cause of encephalitis is a filtrable virus similar to that producing herpes, poliomyelitis, rabies, vaccinia and a number of other diseases.

The final demonstration of the etiologic factor in epidemic encephalitis still awaits the efforts of investigators.

SYMPTOMATOLOGY

Acute Epidemic Encephalitis.—There is no known disease of the central and peripheral nervous system which is capable of producing such an all-inclusive symptomatology as epidemic encephalitis. Until the advent of this disease, syphilis was hailed as the example, par excellence, of an infecting agent capable of producing protean manifestations of involvement of the nervous system, but the recent studies of epidemic encephalitis have produced such a wealth of symptomatic

detail that syphilis pales into insignificance in comparison with this disease as an excitor of varying manifestations of neurologic involvement. The symptoms antecedent to the neural manifestations are those characteristic of any acute or subacute infectious disease and are in no way prophetic of the more serious sequelae that may result. These symptoms are those of a mild catarrhal invasion, with a coryza, chilly sensations, slight fever, malaise, headache, anorexia, dizziness and vague fleeting somatic pains. These symptoms may be entirely lacking or so insignificant as not to attract the patient's attention and in many instances no history of any prodromal period can be elicited. The evidences of the invasion of the nervous system may be extremely violent, consisting of excruciating headache, symptoms of extreme meningeal irritation, mania and death within from twenty-four to forty-eight hours, but the usual course of events is the gradual development of cranial nerve palsies of various types, the appearance of hyperkinetic phenomena, chiefly from involvement of the extrapyramidal systems, progressive paralyses of a lower motor neuron type or the slow evolution of the so-called sequelae, or more correctly the appearance of chronic epidemic encephalitis. An almost constant accompaniment of the invasion of the nervous system is the development of drowsiness or lethargy, which may be so extreme as to submerge all of the patient's volitional activities into a torpitude from which he cannot escape, although he may be acutely conscious of everything which is going on about him.

The symptomatology of this disease is practically coextensive with the functional capacities of the nervous system, for since the disease is capable of localization anywhere within the central and peripheral nervous systems, its manifestations may take the guise of disturbance in any function or part of function of the entire nervous system.

As a general rule, broken in many instances, the nuclear or gray matter of the nervous system seems to be much more vulnerable to the attack of this infecting agent than the white matter. The localization of the disturbance in the cortex is usually manifested by torpor, hebetude, slowness of intellectual function, depression, coma and death, or per contra, restlessness, irritability, excitability, anxiety, euphoria, delirium or maniacal excitement. If the motor cortex is involved, there may be an excitatory phase with localized spasm of the cortical type involving specific movements rather than isolated muscular contractions. These irritative phenomena may take on the form of jacksonian convulsive seizures, or there may be generalized convulsive attacks. This preliminary irritative phase may be absent or very short, and paralytic phenomena may soon appear, such as facial paresis or paralysis of the central type, the musculature about the mouth being involved, a monoplegia affecting one arm or one leg or a hemiplegia. At times the

special functions of speech or writing may be involved independently or in conjunction with other motor manifestations with the production of aphasia or agraphia. The parietal cortex may be involved with the appearance in the irritative phase of hyperesthetic phenomena chiefly of the thalamic type, presenting a marked affective or disagreeable quality, characterized by diffuseness and indefiniteness of localization only to be followed later by the paralytic phase evidenced by gnostic defects, which make themselves apparent by loss of limb sense, defects in localization and the failure to recognize objects by palpation.

The disturbances of the special senses of sight and hearing illustrative of occipital and temporal lobe involvement are less frequently seen, but irritative phenomena characterized by hallucinations of sight and hearing may occur. The paralytic manifestations of hemianopia, either quadrantic or hemianopic, may later appear. The sense of hearing being bilaterally represented is but rarely affected so far as paralytic phenomena are concerned.

Among the remaining cerebral structures, the basal ganglia seem to be selectively affected, this localization taking place chiefly in the more chronic forms and thus being probably due to the paralytic effects of the pathologic process which set lower centers free from the superimposed control of the more recently organized higher functions. These hyperkinetic phenomena supply perhaps the amplest symptomatology of this disease and the various results of this splitting or dissection of voluntary movement have brought out an as yet unanalyzed mass of symptomatic and functional evidence. These manifestations may be of almost any recognized type, choreiform, athetotic, choreo-athetotic or dystonic, with also the development of tics, mobile spasms, tremors, champing movements of the jaws and other abnormal involuntary movements. Associated with these dyskineses, perhaps productive of them, are found all the known forms of tone disturbance, which may appear either as hypertonic or hypotonic phenomena or as combinations of both, producing the dystonic form of abnormal tone distribution. The most common example of basal ganglion involvement is the type universally recognized, the parkinsonian or paralysis agitans form with the mask facies, the loss of associated movements, the hypertonicity and the familiar succession movements of the thumb and finger producing the pill-rolling type of tremor.

Localization in the brain stem may produce involvement of any single motor nucleus or any combination of these nuclei. The sensory nuclear accumulations are but rarely involved. The most commonly seen types are those which bear evidence of the predilection of this virus for the midbrain, for oculomotor involvement is one of the most frequent of all of the manifestations of this disease. One or both oculomotor nerves are often involved, resulting in ptosis of the eyelid,

external strabismus and the inability to move the eye upward, downward or inward. This involvement may be complete or partial, depending on the extent of the pathologic process. The trochlear nucleus may be involved causing disturbances much more difficult to demonstrate clinically, but manifested by diplopia in an oblique plane, a rotation of the eyeball upward and outward, and an inability to move the eyeball downward and outward. Involvement of the abducens nucleus results in an internal strabismus with an inability to move the affected eye outward. The other motor nuclei show involvement much less frequently, but a facial palsy is not an uncommon manifestation. This paralysis may be partial or complete and is of the peripheral, nuclear or infranuclear type involving the entire innervation of the muscles of one half of the face. This may often be bilateral, producing an entire loss of movement of the facial muscles. The motor trigeminal, glossopharyngeal and vagus nuclei are occasionally involved, producing disturbances in mastication, deglutition and phonation.

The cerebellum may be involved in its cortical constituents producing ataxia, asynergia and disturbances in the production of coordinated skilled acts and in the succession movements which are so dependent on an exact integration of the synergic units.

The gray matter of the spinal cord often shows marked involvement by this disease. With this locus of incidence there appear myoclonic or fibrillary tremors depending on the incidence of the destructive influence of the disease on the connector neurons or on the ventral horn cells, the final common pathway. This irritative phase is usually followed later by a paralytic condition which is strikingly similar to the disturbance produced by anterior poliomyelitis except that the condition is usually progressive over a considerable length of time and is often associated with persistent signs of irritation, namely, fibrillary tremors. The focus of this involvement may be in any part of the ventral gray matter and therefore the exact muscular symptomatology will be dependent on the anatomic location or diffusion of the destructive process. The paralytic phenomena following the localization of the disease process in the ventral horn cells are associated with muscular atrophy, loss of substance and contour in the actual muscles or muscle groups involved. In some instances the process is so severe and widespread as to produce an almost total disappearance of all the ventral horn cells in the spinal cord.

The involvement of the afferent structures, particularly the dorsal root ganglia, is characterized in the irritative phase by lancinating pains which may be of any degree from mild rheumatic manifestations to stabbing paroxysms of excruciating severity. Frequently, the evidences of irritative involvement of the dorsal root fibers and the dorsal horn cells may be manifested by dysesthesias resulting in burning, crawling,

blistering or bursting pains. This symptom often precedes the establishment of ventral horn cell symptomatology, giving the impression that the virus gains initial lodgment in the dorsal root ganglia and then passes into the spinal cord to attack the ventral horn cells. The pains are usually dermatomic in location and the area of cutaneous distribution is often homologous with the segmental derivation of the muscles later involved in the hyperkinetic and hypokinetic phenomena. The radicular pains are often followed by herpetic lesions distributed within the same dermatome.

The paralytic phenomena consequent on involvement of the dorsal root ganglia and the dorsal horn of the gray matter of the spinal cord can frequently be demonstrated as diffuse spotty losses of one or another of the superficial types of sensibility which have a partial or total distribution according to the dermatomes which may have been involved. Evidence that other localizations affecting the afferent constituents may take place may be cited in the appearance of herpes labialis and nasalis, the development of neuralgic manifestations in one or more branches of the trigeminal nerve and in the dizziness, nystagmus and past-pointing which are interpreted as evidences of involvement of the afferent vestibular pathways.

Involvement of the intra-axial myelinated pathways is often present in this disease.[35] In connection with the spinal cord, this may manifest itself as single or complicated system degenerations. Wimmer[36] has described a type of spinal involvement by this disease resembling amyotrophic lateral sclerosis, in which a symptom picture of a combined involvement of the ventral gray matter and the lateral white columns may present itself. Other authors have described syndromes resembling tabes and combined sclerosis. In the brain stem this involvement of white fiber systems has aroused a great deal of interest recently; a number of papers have appeared dealing with forced conjugate movements of the eyes.[37] In these spasms the eyes usually turn upward and to one side or the other. In other instances skew deviations appear in which one eye may be turned in one direction, the other assuming an entirely independent axis. The latter phenomenon is usually explained by the assumption of a lesion in the posterior longitudinal fasciculus through which bundle the binocular associations are maintained.

35. Brock, S., and Margaretten, I.: Pyramidal and Extrapyramidal System Involvement in Epidemic Encephalitis, Arch. Neurol. & Psychiat. **8**:660 (Dec.) 1922.

36. Wimmer, A.: Chronic Epidemic Encephalitis, London, William Heinemann, 1928.

37. Pardee, I. H.: Paroxysmal Oculogyric Crises in Parkinsonian Encephalitis, Am. J. M. Sc. **175**:683, 1928. Kennedy, F.: Ocular Disturbances in Epidemic Encephalitis, Arch. Ophth. **1**:346 (March) 1929.

At times, paraplegic lesions or those simulating syringomyelia or transverse lesions may be met with, but these are considered as rather incidental disturbances occasioned by vascular accidents following a weakening of the walls of the blood vessels as a result of the pathology existent in the central nervous system.[38]

The peripheral nerves are occasionally attacked with resulting sensory and motor involvement, the phenomena depending on the particular nerve or nerves involved and presenting in all essentials the picture of a multiple peripheral neuritis.[39]

Papilledema is a rather rare condition in epidemic encephalitis, but one which is found often enough to warrant serious consideration. It is usually of rather mild degree, exhibiting a swelling of from 1 to 2 diopters but occasionally reaching the extent of 4 or 5 diopters.[40] It presents no pathologic characteristics capable of differentiating it from that of increased intracranial pressure, and the entire symptom picture and the course of events must in the last analysis determine this differentiation.

Holden [41] has called attention to a frequent symptom of involvement of the oculomotor apparatus. This is a paralysis of divergence in which the eyes can be focused on an object about 15 cm. in front of the eyes, and at this distance the object is seen singly; beyond this point, however, an homonymous diplopia takes place.

The meninges may show a special vulnerability to the disease, with the early development of acute or subacute signs of meningitic irritation. These symptoms are the classic signs of headache, photophobia, stiffness of the neck, a Kernig sign, the Brudzinski phenomena and the appearance of a marked dermographia. A special type may be recognized in the hemorrhagic form in which are present not only all of the already mentioned signs but also the almost constant appearance of varying amounts of blood in the spinal fluid.

The manifestations of this disease when the chief onus of its incidence falls on the psychic and psychologic functions have been considered by many authors from one standpoint or another. The contribution by Kirby and Davis [42] presents a comprehensive and most

38. Riley, H. A.: The Spinal Forms of Epidemic Encephalitis, Arch. Neurol. & Psychiat. **5**:408 (April) 1921.

39. Pardee, I. H.: An Acute Descending Radicular Type of Epidemic Encephalitis, Arch. Neurol. & Psychiat. **4**:24 (July) 1920.

40. Spiller, W. G.: High Grade Choked Disks in Epidemic Encephalitis, J. A. M. A. **80**:1843 (June 23) 1923.

41. Holden, W. A.: The Ocular Manifestations of Epidemic Encephalitis, Arch. Ophth. **50**:101 (March) 1921.

42. Kirby, G. H., and Davis, T. K.: Psychiatric Aspects of Epidemic Encephalitis, Arch. Neurol. & Psychiat. **5**:491 (May) 1921.

satisfactory résumé of this phase of epidemic encephalitis. The disease in its psychiatric aspects represents an organic attack on the psychologic processes of the brain and manifests itself as a typical toxic-infectious psychosis. The functions impaired by this morbid process affect the apprehension, elaboration, proper orientation and retention of psychic stimuli and their resulting concepts. Not only is the acquisition and elaboration of these primary constituents interfered with, but also, as a result of the disease process, there is a difficulty in the activation of memories and as a result of this defects in comparison develop, and therefore an impairment of the faculties of judgment, reason and the other higher mental processes is prone to appear.

Aside from the more intellectual phases of mental activity, there are interferences with the affective contributions to the total mental function, and oscillations in mood, emotional disturbances of all kinds, manic-depressive tendencies and many other benign emotional disorders may make their appearance. As a result of these deficiencies in the composition and the emotional coloring of the mental faculties, disturbances in the mental trend appear. These may be characterized in brief by unusual attitudes toward the external environment; perverted constitutional peculiarities appear in the psychogenic mechanisms and manifest themselves by schizoid and paranoid states.

Patients suffering from epidemic encephalitis present an extreme variability in their level of consciousness, torpor and hebetude at one extreme being contrasted with delirium and maniacal excitement at the other. The degree of attention constantly fluctuates. It can be aroused and held by a distinct effort of the examiner, but when this is relaxed the patient relapses into a state of inattention, his psychic function becoming absorbed in his own perverted activities, often with the appearance of a muttering incoherence. With this clouding of consciousness and the failure of attention, dreamlike states appear which are permeated by hallucinatory processes and colored by the habitual or pathologic trends of the patient.

In many instances the psychomotor retardation becomes so excessive that a mild or even marked degree of catatonia, with a "waxy flexibility," makes its appearance. This is similar to that seen in the schizoid reaction types.[43]

The occurrence of narcolepsy has been mentioned by observers such as Spiller [44] and Adie.[45]

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43. Strecker, E. A., and Marsh, F. B.: A Case of Epidemic Encephalitis with Unusual Features, J. A. M. A. **76**:777 (March 19) 1921.

44. Spiller, W. G.: Narcolepsy Occasionally a Post-Encephalitic Syndrome, J. A. M. A. **86**:673 (March 6) 1926.

45. Adie, W. J.: Idiopathic Narcolepsy: A Disease sui Generis; with Remarks on the Mechanism of Sleep, Brain **49**:257, 1926.

The toxic-infectious psychosis often manifests marked resemblance to the typical psychoses of this category, that is, the amnesic-confabulatory form of Korsakoff. This has been mentioned by Kirby and Davis [42] and it has also received a considerable degree of attention by Barker.[46] This author also emphasized the extreme restlessness and irritability which characterize these patients. He also stressed the mood disturbances and the depression which is often one of the most distressing features in the disease. In a patient at present under my own observation, this restlessness and at the same time an almost insurmountable inertia combine to supply practically an unbearable tedium to life. There is a restless, constant urge to psychomotor activity with, at the same time, a deadening load of lethargy and almost painful disinclination to any activity of any kind. The constant conflict between these two features has turned a full useful life into one of unending torture.

The behavior disturbances which follow this disease in children are of great interest and importance. These disturbances have been well dealt with by Barker, Happ and Blackfan,[47] Collin and Requin,[48] Leahy and Sands [49] and Anderson.[50] These authors emphasized the disordered mentality and the perverted psychic and psychomotor reactions which follow in the train of epidemic encephalitis when it attacks the child and the adolescent. There is marked irritability and restlessness associated with purposeless impulsive acts, such as spitting, grimacing and explosive breathing. There are marked disorders of attention, with distractability and disorder in the mental production. The emotional status is greatly altered, with a marked changeability and inadequate and inconsistent affective reactions. Prominent among the symptoms have been a precocity of sexuality and intense eroticism.

The disposition of these children undergoes a profound change, characterized by disobedience, unprovoked fits of temper, cruelty to associates and to animals, marked destructiveness, kleptomania, mental impairment and retardation.

Almost constantly, disturbances of sleep appear; they may vary from an excessive drowsiness to almost complete sleeplessness. In many instances drowsiness during the day and sleeplessness at night have characterized this aspect of the disease.

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46. Barker, L. F.: The Sequelae of Epidemic Encephalitis, New York State J. Med. **22**:251, 1922.

47. Happ, W. M., and Blackfan, K. D.: Insomnia Following Acute Epidemic (Lethargic) Encephalitis in Children, J. A. M. A. **75**:1337 (Nov. 13) 1920.

48. Collin, A., and Requin, J.: Sequelles psychiques de l'encéphalite épidémique chez les enfants, Arch. de méd. d. enf. **26**:265, 1923.

49. Leahy, S. R., and Sands, I. J.: Mental Disorders in Children Following Epidemic Encephalitis, J. A. M. A. **76**:373 (Feb. 5) 1921.

50. Anderson, G. M.: The Sequelae of Lethargic Encephalitis in Children, Quart. J. Med. **16**:173, 1922-1923.

The evidences of the involvement of the autonomic nervous system are almost constant. Disturbances in generalized perspiration and vasomotor control are practically universal. This usually manifests itself as an excessive perspiration, a peculiar oily condition of the skin, marked vasomotor irritability, with flushing of the skin and also associated pilomotor phenomena and the production of goose flesh. The secretion of saliva is greatly increased and may become a distressing feature of the disease. Disturbances in taste may appear. Tachycardia or bradycardia may be a prominent symptom. With the latter is usually associated a marked asthenia and a low blood pressure. An interesting but distressing manifestation is the disordered condition of the respiratory system. This may manifest itself as a hyperpnea, with forced holding of the breath and explosive respiration, while in other cases a bradypnea or other respiratory disturbances may appear.[51] Hiccup has been described in many instances, and in certain localities and times it has attained the condition of an epidemic. Whether the irritation lies in the sphere of the afferent vagus or the efferent phrenic nerve is not definitely established. A form of this was described by Halbron and Gambillard[52] as a myoclonus of the diaphragm. The pupillary and accommodative subdivisions of the oculomotor nucleus are extremely susceptible to involvement by the virus of epidemic encephalitis. A paralysis of lenticular accommodation is present in about 35 per cent of the cases. The pupils are usually somewhat or widely dilated; they are frequently unequal, fairly regular and react better to light than they do in accommodation thus differing from the Argyll Robertson pupil of tabes dorsalis.

In many instances there is evidence of the effect of this disease on the central ganglia controlling the activity of the autonomic nervous system. This is usually interpreted as an involvement of the hypencephalic portion of the brain, the structures forming the floor of the third ventricle. This manifests itself by disturbance in metabolism, temperature regulation, vasomotor control, the ingestion and excretion of fluid and the maintenance of body weight. Postencephalitic obesity is a result which has often followed involvement of this part of the brain. This condition has been attributed to a disordered condition of the pituitary gland,[53] the chief accretions of adipose tissue being about the pelvic girdle and the thighs.

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51. Pardee, I. H.: Spasmodic Forced Respiration as a Sequel of Epidemic Encephalitis, J. A. M. A. **80**:178 (Jan. 20) 1923. Payne, G. C., and Armstrong, C.: Epidemic Transient Diaphragmatic Spasm, J. A. M. A. **81**:746 (Sept. 1) 1923.

52. Halbron, P., and Gambillard, M.: Myoclonie du diaphragme d'origine encéphalitique, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:95, 1924.

53. Walsh, T. G.: Postencephalitic Obesity: Report of Cases, J. A. M. A. **87**: 305 (July 31) 1926.

The subarachnoid fluid in the acute or subacute phases of this disease shows some deviation from the normal in from 70 to 75 per cent of the cases. The fluid is usually clear and colorless, except in the hemorrhagic meningitic types when it may be yellowish, opalescent or frankly bloody in appearance. The pressure is often greatly increased, ranging from 200 to 300 mm. of water pressure. There is usually no evidence of block in the subarachnoid passageways.

The cells are often increased, the number usually varying between 10 and 250 per cubic millimeter. The globulin is slightly increased, varying from 25 to 50 mg. per hundred cubic centimeters of fluid. The sugar content is usually increased above 80 mg. The colloidal gold curve may show all types of reaction from the normal row of zeros through the curve characteristic of cerebrospinal syphilis, 1112211000, to the paretic type of 5555543210.

There is usually a mild febrile movement varying from 100 to 102 F., although hyperpyrexia may be present. The blood count shows a slight leukocytosis with a slight increase in the polymorphonuclear leukocytes. The urine is usually normal.

Chronic Epidemic Encephalitis.—While the symptomatology of acute encephalitis is of great interest to the clinical and research investigator, it is equaled, if not surpassed, by the fascination aroused by the enduring signs of this disease. These signs have been labeled and analyzed in many exhaustive contributions under the title of postencephalitic types of sequelae.[54] From time to time, however, a certain amount of dissatisfaction has been evinced over this title with its connotation of a completed, burned-out picture, characterized by a static condition and the implication of a final conclusion. The recent considerations of this phase of the disease have turned more to the conception of a continuing process, one which in many instances may produce an apparently definitive form, but in many others takes on itself a mutational aspect first bearing one and then another imprint. Many examples continue to manifest a slow, relentless progression which successively destroys one function after another until death brings the tragedy to a close. Schaller and Oliver,[55] writing in 1922, reported a case under the title of chronic epidemic encephalitis, which lasted over a period of fourteen months. This case finally came to postmortem examination and instead of showing the usual pathologic appearance of a degenerative encephalopathy, it presented the morbid appearance of an inflammatory reaction in all stages and grades of tissue activity. Areas of the

54. House, W.: Sequelae of Epidemic (Lethargic) Encephalitis, J. A. M. A. **79**:211 (July 15) 1922.

55. Schaller, W. F., and Oliver, J.: Chronic Epidemic Encephalitis, Arch. Neurol. & Psychiat. **8**:1 (July) 1922.

nervous system were found which presented the picture of a healed process with dense masses of gliogenous tissue, consisting chiefly of a matted feltwork of glia fibers, in the interstices of which appeared many amylaceous bodies and only an occasional glia cell. In other parts of the brain were found areas of acute inflammatory reaction with hemorrhages, perivascular infiltration with round cells, including lymphocytes, plasma cells and a few "endothelial leukocytes." In the larger cells were found numerous coarse fat deposits. Adventitial proliferative changes were also present, with an increased number of fusiform cells with large vesicular nuclei and intercellular collagen fibers. An occasional example of Nissl's acute type of degeneration, with eccentricity of the nucleus and chromatolysis of the tigroid bodies, was found. Satellitosis, as well as neuronophagia, was frequently seen, while many shadow forms were present. Von Economo [56] reported similar observations, as did Globus and Strauss,[57] who described the condition as a subacute form presenting lesions of mixed acute and chronic pathologic character. The presence of pathologic changes of a chronic character would seem to throw doubt on the validity of terming such a condition subacute and would rather strengthen the view that this disease is never a completed story, but that it retains the possibility of flaring out after the passage of months or even years into renewed activity, not as fresh attacks but rather as regional resurgences into an active destructive process.

Freeman,[58] in 1926, gave this view greater emphasis and he stated that clinical, pathologic, bacteriologic and epidemiologic evidence points to the late manifestations of this disease as being the results of a persistent causative agent, active long after the subsidence of the acute infection. He expressed the belief that patients presenting the so-called sequelae of the disease are but developing changing manifestations of a continuing disease and not the results of a slow degeneration following the initial destructive activity of the acute attack. A patient who has been under my observation for more than four years has presented typical evidences of a continuing infection which first presented itself as an acute equilibratory disturbance associated with lethargy, depression, psychomotor retardation and mild ataxia in the left upper extremity and vague sensory disturbances over the inner surface of the thighs. Almost two years later, an acute sensory disturbance with complete loss of sensation developed over the sacral dermatomes and the rectum

56. Von Economo, C.: Encephalitis lethargica subchronica, Wien. Arch. f. inn. Med. **1**:371, 1920.

57. Globus, H. H., and Strauss, I.: Subacute Epidemic Encephalitis, Tr. Am. Neurol. A. **47**:370, 1921.

58. Freeman, W.: Chronic Epidemic Encephalitis, J. A. M. A. **87**:1601 (Nov. 13) 1926.

and vagina, with only mild motor symptoms. This hypesthesia was associated with the most intense paresthesia over the soles and the dorsal aspects of the calves, thighs and buttocks, with a most extreme aching and discomfort in the bones, joints and muscles. This condition has slowly extended upward to involve the lower six thoracic dermatomes while the sacral dermatomes have returned almost to normal.

The frequent history of these clinical cases with, as Freeman pointed out, latent periods, remissions, exacerbations and progressive involvement of one system after another, points to a persistence of the causative agent, in many instances manifesting an increasing disablement and eventuating in death. He believed that the marked evidences of destruction, the widespread scattering of pigment, the appearance of wandering glia cells, the overgrowth by a gliogenous feltwork and the presence of fat in the scavenger cells years after the active onset of the disease show that the activating agent is still producing pathologic and clinical evidence of persistence.

Hohmann [59] commented on the universal discovery in his cases of evidence of persistent acute and subacute inflammatory reactions, even after months and years of the disease. Scholz [60] and Meggendorfer [61] also emphasized this point.

Freeman cited several cases collected from the literature in which persons apparently contracted this disease through close association with patients who were suffering from a chronic form of the disease or who were in an acute exacerbation.

Price,[62] describing the residual late manifestations and atypical forms of the disease, emphasized the chronic progressive character of the disease and described a case in which a relapse developed seven years after the initial attack. He emphasized the persistent chronic character of the infection.

From these published reports by careful observers and from the irrefutable evidence which is presented in most of the reliable pathologic discussions of this disease, it might therefore seem wiser to use with greater care the terms "postencephalitic" and "sequelae," and restrict them to the instances of the disease which present enduring evidences of arrest or cure. Even with these cases the future alone can deal, for

59. Hohmann, L. B.: Histopathology of Postencephalitic Parkinson's Syndrome, Bull. Johns Hopkins Hosp. **36**:403, 1925.

60. Scholz, W.: Zur Klinik und pathologischen Anatomie der chronischen Encephalitis epidemica: Ein Fall mit Parkinismus und schwerer corticaler Sehstörung, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:533, 1923.

61. Meggendorfer, F.: Chronische Encephalitis epidemica, Ztschr. f. d. ges. Neurol. u. Psychiat. **75**:189, 1922.

62. Price, G. E.: Epidemic Encephalitis: Residua, Late Manifestations and Atypical Forms of the Disease, J. Iowa M. Soc. **16**:395, 1926.

there is no assurance that even these cases may not at some later date bring forth new evidences of the persistence of the etiologic agent. There is definite evidence in many of the cases coming to postmortem examination that by no stretch of the imagination could the pathologic data be interpreted as postencephalitic degenerative changes or sequelae of the preceding acute process, for the cellular observations can be interpreted only in the light of a persistent progressive morbid process.

Wimmer,[36] in his collected studies, emphasized the occurrence of convulsive seizures in chronic epidemic encephalitis. He stated that these attacks may develop out of the acute initial lethargic state or may appear only after a free interval of from six months to eight years; the majority of his cases developed from four to six years after the initial attack. The convulsive seizures may be unilateral and continue as such, or they may gradually merge into generalized convulsions. He attributed these phenomena to the inflammatory or so-called "degenerative" changes which are so commonly seen in postmortem studies.

Grossman's[63] investigation of ninety-two cases showed that there was a mortality of 20 per cent. This report covered a period of several years in which the intensity of the disease underwent a considerable abatement. The mortality of the Winnipeg epidemic of 1919 (Boyd[1]), in seventy-five cases, was 39 per cent. Reference has already been made to later mortality figures. Grossman's figures showed that as far as the cases were followed, ten patients recovered completely, fourteen sufficiently to return to work with some residuals, such as cranial nerve pareses, insomnia, irritability, depression, restlessness or headache, while sixty-two showed some form of progressive neural involvement. Of this group of cases, forty-two patients presented the so-called postencephalitic parkinsonian type of involvement.

G. Levy, in reporting cases from the clinic of Marie, described 129 cases with sequelae. He also indicated the marked preponderance of the parkinsonian type, of which there were seventy instances. Forty-three others presented excitomotor manifestations, such as chorea, myoclonus, convulsive seizures, rhythmic masseteric spasms, tics, tremors, palsies, restlessness and tonic eye spasms.

Symptomatic Grouping of Cases.—By virtue of the localization of the major incidence of the destructive process it is possible to make a more or less satisfactory grouping of the sequelae and the clinical forms. Pure symptomatic pictures are rare and as a rule the evidences of dissemination may be discovered in almost every case, but the accompanying schema may illustrate the major anatomic and symptomatic groups.

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63. Grossman, M.: Sequels of Acute Epidemic Encephalitis, J. A. M. A. **78:** 959 (April 1) 1922.

Types: Neurologic

A. Cortical and Subcortical

1. Kinetic:
   (*a*) Irritative: general or local convulsive seizures
   (*b*) Paralytic: monoplegia, hemiplegia or tetraplegia, aphasia, agraphia
2. Esthetic:
   (*a*) Irritative: parietal, temporal, occipital, rhinencephalic hallucinosis
   (*b*) Paralytic: Hypesthesia or anesthesia; hemianopia; quadrantic, homonymous, etc.

B. Basal Nuclear:

1. Kinetic:
   (*a*) Choreiform, choreo-athetotic, athetotic, dystonic, parkinsonian (with or without tremor), champing, tic, spasm, progressive lenticular (Wilson's)
2. Esthetic:
   Thalamic, hyperesthetic-anesthetic

C. Hypencephalic:

1. Retrobulbar, neuritic
2. Hypopituitary (Fröhlich's)
3. Central neurovisceral

D. Brain Stem:

1. Kinetic:
   (*a*) Irritative: (*a*) Oculogyric and oculocephalogyric
   (*b*) Masticatory
   (*c*) Facial tic
   (*d*) Deglutitional
   (*b*) Paralytic: (*a*) Polio-encephalitis superior, III, IV, VI
   (*b*) Polio-encephalitis inferior, V, IX, X, XII
2. Esthetic:
   (*a*) Irritative: neuralgic
   (*a*) Trigeminal
   (*b*) Acoustic: vestibular, cochlear
   (*c*) Glossopharyngeal
   (*b*) Paralytic:
   (*a*) Trigeminal
   (*b*) Glossopharyngeal

E. Cerebellar: ataxic, asynergic

F. Spinal:

1. Irritative:
   (a) Dorsal poliomyelitic, herpetic
   (*b*) Radicular; neuralgic, hyperesthetic
   (*c*) Ventral poliomyelitic; myoclonic, fascicular
2. Paralytic:
   (*a*) Dorsal poliomyelitic and radicular; hypesthetic, anesthetic
   (*b*) Ventral poliomyelitic: amyotrophy and paralysis
   (*c*) Myelitic:
   (*a'*) Dorsolateral sclerotic
   (*b'*) Transverse—partial or complete
   (*c'*) Disseminated
   (*d'*) Combined—amyotrophic lateral sclerotic

G. Neuritic:
1. Motor
2. Sensory
3. Combined

H. Autonomic:
1. Parasympathetic:
   (*a*) Mesencephalic—pupillary and ciliary
   (*b*) Bulbar: Salivary
   Pneic—bradypneic, polypneic, dyspneic
   Cardiac—bradycardia, tachycardia
   Enteric—spasmodic
   (*c*) Pelvic: Vesical—retention, incontinence
   (*d*) Sexual: impotence, eroticism
2. Sympathetic:
   Enophthalmic; Horner's type
   Sudorific; anhidrosis, hyperhidrosis
   Vasomotor

I. Myasthenic

J. Meningitic

K. Neoplastic

L. Psychic
   (*a*) Somneic—lethargy, hypersomnia, hyposomnia and inverted sleep
   (*b*) Delirious—confusional
   (*c*) Manic-depressive
   (*d*) Amnesic—confabulatory
   (*e*) Mixed trends—phobic, compulsive, paranoid, emotional, degenerative
   (*f*) Behavioral disturbances

M. Endocrinic
   (*a*) Thyroid
   (*b*) Suprarenal

N. Mixed forms

DIAGNOSIS

Before the essential character of this disease was well understood, the early cases were diagnosed as botulism, toxic ophthalmoplegia, acute polio-encephalitis, bulbar paralysis, poliomyelitis and a host of other neurologic conditions.[64] As a rule, the diagnosis depends on the presence of a low grade infectious process, associated with lethargy, diplopia, headache and, most important of all, evidence of dissemination of the lesions throughout the length and breadth of the nervous system. The diagnosis of the chronic or later manifestations usually depends on the identification of some influenza-like infection which may have preceded the more slowly developing symptomatology of the disease by an interval which may vary between six months and seven years. The

64. Encephalitis Lethargica: A New Disease? Editorial, J. A. M. A. **72**:414 (Feb. 8) 1919.

establishment of the existence of widespread lesions producing diversified combinations of neural signs usually suffices to establish a definite suspicion of an epidemic encephalitis.

Cerebrospinal Syphilis.—Syphilis, of course, is one of the most important factors which must be eliminated, as it is the undisputed claimant to second place among those agents which are capable of presenting a kaleidoscopic conglomeration of neurologic manifestations. In this differentiation, the Wassermann reaction offers the most reliable criterion, for the lesions and symptoms of both may be almost identical.

Cerebral Neoplasm.—The differential diagnosis between epidemic encephalitis and brain neoplasm often offers considerable difficulties. The examination of the spinal fluid may not supply any evidence of value, for in both conditions may be found an increase of pressure, a raised cell count and chemical changes, or in both no characteristic disturbances may be detected. In the last analysis the history, the evidence of dissemination of the lesions, the lethargy and above all the clinical course of the disease are the characteristics that may serve to establish the differentiation.

Cerebral Abscess.—An even more difficult differential diagnosis to make is that between epidemic encephalitis and abscess of the brain. In this situation, the history of some antecedent infectious process somewhere within the body, especially within the accessory spaces of the head, may serve to establish the localized form of involvement, while the evidence of dissemination may aid in establishing the diagnosis of a diffuse process affecting the nervous system.

Anterior Poliomyelitis.—It is often difficult to differentiate between the spinal form of epidemic encephalitis and acute anterior poliomyelitis, especially when the more general symptoms of the former are absent. In considering the local neural manifestations, the clinical course is usually quite different, poliomyelitis presenting a fulminating incidence with progressive improvement, whereas epidemic encephalitis is usually insidious in onset and progressive at least to a limited extent. Epidemic encephalitis is usually associated also with a good deal of preliminary pain which is radicular in distribution, and the muscles are usually not tender, whereas in poliomyelitis there is usually little pain, and muscular tenderness is almost a constant manifestation of the disease. The presence of myoclonic or fibrillary twitchings serves to supply a useful point in differentiation, since they are almost constant in encephalitis and practically never present in poliomyelitis.

Meningitis.—In differentiating between encephalitis and meningitis, the laboratory examination of the spinal fluid, in the final analysis, offers the only true diagnostic differentiation. Cultural studies in many instances are the means by which a definite distinction may be

made, since the clinical picture of the two diseases may be identical. One fact may be of some importance, however—the greater tendency for free blood to be found in the spinal fluid in encephalitis, whereas it is relatively rare in the acute and chronic forms of meningitis, except in that unusual form of chronic meningitis called progressive proliferative hemorrhagic pachymeningitis; but in this the alcoholic or syphilitic character of the patient and the age incidence, the patients with meningitis being more uniformly older, will be of considerable aid in the diagnosis.

There can be no question, however, that the diagnosis of epidemic encephalitis has offered a refuge which serves in many cases as a cloak under which one often attempts to hide ignorance or inability to reconcile the results of examinations. The facile ability of this disease to ape any of the well known syndromes of nervous involvement is so omnipresent that the temptation is well nigh irresistible to call any puzzling combination of signs of neural involvement by this name. Therefore, in the name of diagnostic honesty every effort should be made to exhaust all means of diagnosis and to invoke every other possible etiologic factor before resort is made to this diagnosis.

COURSE

The average incubation period seems to have been definitely fixed by Boyd, through his observation of patients who visited where there were known foci of contagion, returned to places uninfected and developed the disease after fourteen days. The onset may present an acute type in which the symptoms develop in an acutely fulminating manner, resulting in death within from twenty-four to forty-eight hours. This type often presents the characteristic of a wild maniacal delirium in which the patient wears himself out in a relatively short time. The subacute type presents the usual manifestations of an invasion by any acute infectious disease, with a period of general malaise, some gastrointestinal symptoms, catarrhal manifestations affecting the respiratory system, a mild grade of fever and headache. Within a short time, the evidences of neural invasion make themselves apparent, with restlessness and irritability, or a gradually increasing lethargy which may completely dominate the picture, the patient sleeping day and night. He can usually be roused, but lapses at once back into his somnolent state. In other instances, the lethargy is replaced by an inability to sleep or the usual association of the day with an alert consciousness and the night with sleep is reversed, and the patient spends his nights in wakefulness and sleeps during the day. This has been termed "an inversion of the sleep curve." This lethargy when it is present is one of the most characteristic manifestations of the disease, the patient lying

immobile, the face presenting the appearance of a death mask, the hands motionless at the sides or crossed over the chest, the movements of respiration and flickering movements of the eyelids being the only evidences of life. Consciousness at the time may be clouded or may be abnormally acute, the patient being in the most distressingly direct contact with his surroundings, unable to make any sign of life but acutely conscious of his condition, often with tears coursing down the cheeks. Some manifestations of oculomotor involvement usually appear, the patient often complaining of diplopia, which is usually of the horizontal type due to involvement of one of the abducens nuclei. In this stage there may appear almost any of the multitudinous symptoms that may result from the varying localizations of the disease. To recapitulate, then, would be but an attempt to list all of the functions of the nervous system. During this stage, the situation may develop for either the better or the worse, with a gradual subsidence of the general and neural disturbances and return to either a normal state or one modified by any degree of enduring disturbance of any one of the functional systems involved by the pathologic process; or the lethargy may increase; one after another the various functional units may be overwhelmed by the etiologic agent, and death may ensue from exhaustion, inanition or progressive neural involvement. Of those who survive, a goodly proportion show some evidences of a continuing progressive disease which may develop along any one of the lines indicated in the analysis of the chronic types of this disease.

PATHOLOGY

The essential pathologic features underlying these manifestations of the symptomatology of this disease are simple: There are, in the acute cases, the same manifestations that characterize all of the nonsuppurative and nonspecific inflammations of the brain. The meninges are reddened and slightly thickened, the tissue fluids are increased and small patches of actual meningitis may be observed. There is a striking tendency toward the production of minute petechial hemorrhages. There is a widespread perivascular infiltration with cells, chiefly lymphocytes, plasma cells and some proliferation of the adventitial cells. The perivascular infiltration often reaches the proportions seen in poliomyelitis and cerebrospinal syphilis. Edema throughout the nervous system is a constant manifestation of this disease.

Claude and Cuel [65] had an opportunity to examine three cases post mortem and confirmed the pathologic changes which have been described by those who have investigated the morbid appearances produced by

65. Claude, H., and Cuel, J. J.: Trois cas d'encéphalite épidémique avec examen anatomique, Encéphale **21**:272, 1926.

this disease. They emphasized especially the widespread diffusion of the disease throughout the central axis and its coverings. They drew attention to the fact that this extreme dissemination of the morbid activities of the disease renders an accurate anatomic localization impossible. From these studies they came to the conclusion that the disease exists as an active invasive process much longer than was formerly believed. This renders more understandable the persistence of symptoms and the slow advance of the clinical manifestations of involvement.

Uchiyama [66] examined six cases after death and in general corroborates the well known pathologic features of the disease. In his cases, the meninges presented a sanguineous or serous exudate in which were found many polymorphonuclear cells, in some instances so extensive as to amount to a purulent exudate. He noted the existence of focal necrosis scattered through the layers of the cortex. He reported that the perivascular infiltration was very marked particularly in the ependymal lining of the ventricles and in the cortex. He also found sclerosis of the blood vessels and bloody extravasations scattered widely through out the nervous system. He described the usual cellular changes indicative of an acute, subacute or chronic process, with the presence of considerable quantities of pigment.

The systemic character of the disease is often manifested, in the more acute types, by the tendency to hemorrhages throughout all of the serous membranes of the body. Nonspecific degenerative changes are often found in the parenchyma of the kidney. In the older cases, the later effects of involvement of the nervous system are always found —satellitosis, neuronophagia, shadow cells, widespread dissemination of formerly intracellular pigments and the gradual disappearance of the cellular elements, associated with the evidences of their disintegration, fat-granular scavenger cells, the so-called gitter cells, and the destruction and removal of the axon and its myelin covering. The replacement features are those which are seen in all destructive and degenerative processes, namely, the appearance of abnormal amounts of gliogenous tissue, at first cellular, at the last fibrillar in character. The areas of major involvement depend on the site of incidence of the full force of the infecting agent and may be in any part of the nervous system. The main areas that seem by predilection to suffer chiefly are the basal ganglia, the structures in the wall of the aqueduct of Sylvius and the cerebral nerve nuclei.

TREATMENT

When one stops to consider that in the treatment for epidemic encephalitis about 600 medicaments or methods of treatment have been

66. Uchiyama, T.: Pathological Studies of Encephalitis Epidemica of 1924 in Japan, Japan M. World **5**:345, 1925.

tried, recommended, enthusiastically tested and then forgotten, the elastic state of the therapeusis for this disease may be readily appreciated. It is an idle gesture even to attempt to review the methods that have been so vigorously acclaimed by some, while in the hands of others they have been productive of nothing but disappointment.

In the recent cases or those exhibiting recrudescenses or exacerbations, one absolutely invariable line of therapy should be rigidly insisted on, namely: complete and utter rest, both physical and mental. On this point too much emphasis cannot be placed. The patient should be allowed to carry on only those physiologic functions which are indispensable to life itself. In addition to this complete negation of all physical and psychic activity, there are three measures, two physical and one medicinal, which have appeared frequently to modify favorably the ordinary course of this malady: (1) The institution of one or another of the dehydrating processes which are effective in the removal of fluid accumulations in the body. The best and most satisfactory is the use of daily injections of 250 cc. of a 25 per cent solution of dextrose, U. S. P., given intravenously. This method has been proved efficient in reducing the amount of spinal fluid and other tissue fluids within the nervous system, so that often the strangling pressure of tissue fluid may be removed from the delicate cellular elements, allowing them to struggle on and ultimately recover at least some measure of function; whereas, if unaided, they might have fallen victim to the purely physical effects of the pathologic process. If the intravenous type of administration is impossible or not advisable, similar though less satisfactory results can be obtained from enemas of magnesium sulphate given in a 50 per cent solution by rectum every day or every other day. (2) Repeated thorough spinal fluid drainage. In the early period of the infection this should be carried out every day as long as the spinal fluid level remains above from 50 to 60 mm. of fluid pressure. When the level falls below this, the operation should be carried out every two, three or four days for a considerable length of time. This method alone has in numerous instances appeared to bring about a considerable amelioration of the symptoms. Whether this results from the purely mechanical removal of pressure or from the elimination of that much toxic material is a subject of debate. (3) The use of the salicylates, given preferably by the rectal route, in maximum dosage. By this method as much as 100 or 200 grains (6.5 or 13 Gm.) of sodium salicylate may be given with apparently beneficial results. If given in a starch enema, 1 drachm (3.9 Gm.) of the salicylate to 1 pint of starch solution, it can be continued for considerable lengths of time without unduly irritating the bowel.

In the subacute and early chronic phases, some favorable reactions have been obtained by the subcutaneous or intravenous injections of

vaccines of almost any known organism in sufficient quantity to produce a sharp nonspecific protein reaction, which by some inexplicable method seems to be able to bring amelioration of symptoms or even an improvement in the clinical picture. Aside from these two procedures, the treatment for this condition is almost purely symptomatic, by means of physical therapeutic agents or medicaments. Much relief can be obtained by massage and the various types of thermic applications. In the distressing tremors, recourse can be had to scopolamine, but usually after the passage of some time this remedy loses its efficiency and the tragic course of the patient continues. It is often possible to prolong the action of these atropine derivatives by changing from one form to another.

The proper and scientific handling of the disease awaits the efforts of epidemiologists and bacteriologists. Until the cause is discovered and isolated, the hands of therapeutists will be tied. At present, the chief emphasis in therapeusis should be placed first on efforts to minimize the destructive effects of the disease by rest, dehydration and thecal drainage, and in the later cases to combat the results of destroyed neural tissue and palliate the distressing results of disturbed nerve function. When bacteriologists and immunologists can produce a specific immunizing serum or antibody extract, then and then only will it be possible for the physician to give battle to one of the most devastating diseases to which human flesh is heir.

PROGRESS IN PSYCHIATRY

IV. EXPERIMENTAL TYPE PSYCHOLOGY *

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The application of methods of experimental psychology to psychiatric problems reached its lowest ebb in the years following the death of Wundt in 1920. It seemed that whatever experimental psychology might have contributed to psychiatry in the past, there were few modern problems amenable to psychologic experiment. In this state of affairs a great change took place after the description of Kretschmer's constitutional types. Since the investigation of about 4,000 cases by different observers and in different parts of the world, a few facts of this system of somatoscopic types have become common property of scientific psychiatric thought, although undoubtedly a large part is still hypothetical and in need of verification and correction. Under the influence of this renewed interest in constitutional types and the new facts established, there has come about a veritable renaissance of experimental psychologic methods in psychiatry. These new and important researches cover a field spoken of as "experimental type psychology."

The pioneer investigations of experimental type psychology, the scope of which is to be outlined in this article,[1] came for the most part from the clinics and laboratories of Wiersma at Groningen, Kretschmer at Marburg, Kroh [2] at Tübingen, and from Russian authors. The first extensive statements were published by van der Horst [3] in 1924, and the main results of these and subsequent investigations were theoretically elaborated by Kretschmer.[4]

* Submitted for publication, Jan. 31, 1930.

1. The so-called eidetic phenomena, which may have a relationship to somatopsychic types, are not included here. Their significance for psychopathology will be considered in a later paper.

2. Kroh, O.: Experimentelle Beiträge zur Typenkunde, in association with G. Bayer, K. Dambach, A. Lutz and O. Vollmer, Ztschr. f. Psychol., 1929, vol. 14; Experimentelle Typenforschung, Deutsche med. Wchnschr. **55**:600, 1929.

3. Van der Horst: Constitutietypen bij Geesteszieken en Gezonden, Zutphen (Holland), Nauta u. Comp, 1924; Experimentelle psychologische Untersuchungen zu Kretschmer's „Körperbau und Charakter", Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:341, 1924.

4. Kretschmer, E.: Der Körperbau der Gesunden und der Begriff der Affinität, Ztschr. f. d. ges. Neurol. u. Psychiat. **107**:749, 1927; Der heutige Stand der psychiatrischen Konstitutionsforschung, Jahresk. f. ärztl. Fortbild. **18**:29, 1927; Experimentelle Typenpsychologie. Sinnes- und denkenpsychologische Resultate, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:776, 1928; Körperbau und Charakter, ed. 7-8, Berlin, Julius Springer, 1929.

The possibility of applying psychologic tests to complex phenomena of the personality rests on the fact that various series of statistical data are available for the calculation of correlations. These are: the clinical diagnoses of the "constitutional" psychoses (manic-depressive psychosis and schizophrenia), the diagnoses of body types from observation alone (somatoscopic diagnoses), the diagnosis of body types from indexes (somatometric diagnoses) and the diagnoses of personality types either from objective observation and examination or from the so-called auto-diagnostic experiments (in which the subject answers a series of questions formulated with a view to eliciting the preponderance of cyclothymic or schizothymic traits.[5] The distinction between cyclothymic and schizothymic types (extroverts and introverts, syntropic and idiotropic, extra-tensive and introversive) had been mainly on a descriptive level. It is the endeavor of experimental type psychology to reduce these sweeping classifications of traits to more closely analyzed and simple—not to say elementary—phenomena.

A forerunner of the investigations by strictly experimental methods was the application of the Rorschach test to Kretschmer's types. In this test the subject is shown a series of meaningless pictures such as may be obtained by folding a piece of paper with black and colored blots on it.[6] He has to describe everything that he can see in these pictures. The Rorschach test is not exact, its interpretation has a large subjective element, and the test, on the whole, is on the borderline between an experimental and a descriptive-intuitive procedure.[7] When critically evaluated, however, it permits surprisingly close characterizations of individuals. Munz [8] applied the Rorschach test to a group of 100 mentally well subjects, of pyknic and leptosome (asthenic) physical types. He found remarkable differences between them. The leptosome

5. Van der Horst (footnote 3, second reference). Kibler: Experimental-psychologischer Beitrag zur Typenforschung, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:524, 1925.

6. The blot-pictures of the Rorschach test consist of a series of carefully planned arrangements of forms and color designed to be shown in a definite sequence (Rorschach, H.: Psychodiagnostik, Leipzig, Ernst Bircher, 1921; The Application of the Interpretation of Form to Psychoanalysis, J. Nerv. & Ment. Dis. **60**:225 and 359, 1924).

7. Loepfe, A.: Ueber Rorschach'sche Formdeutversuche, Ztschr. f. ang. Psychol. **26**:202, 1926. Binswanger, L.: Bemerkungen zu Hermann Rorschach's „Psychodiagnostik," Internat. Ztschr. f. ärztl. Psychoanal. **9**:512, 1923. Müller, M.: Der Rorschach'sche Formdeutversuch, seine Schwierigkeiten und Ergebnisse, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:598, 1929. Kretschmer, E.: Medizinische Psychologie, ed. 3, Leipzig, Georg Thieme, 1926.

8. Munz, E.: Die Reaktion des Pyknikers im Rorschach'schen psychodiagnostischen Versuch, Ztschr. f. d. ges. Neurol. u. Psychiat. **91**:27, 1924; abstr., J. Ment. Sc. **71**:329, 1925.

individuals described the pictures in a dry, sometimes pedantic, fashion. They had more "kinesthetic answers"; that is, they described more forms of persons or animals in definite postures or movements. They saw more unreal configurations, faces, masks and figures. They described various heterogeneous, logically uncombined details in the same picture, and showed less tendency than the pyknic individuals to see in the same blot-picture as a whole one unitary form (e. g., a landscape). The pyknic individuals, on the other hand, described the pictures more naively and with more emotion. They tended to be more influenced by colors ("color answers") and effects produced by light and shade. They described more objects and landscapes, and had a tendency to combine the whole blot-picture into one unitary complex with reference to which they described details. Further, the leptosome type tended to give a larger percentage of "whole" answers (the entire blot-picture or the greater part of it seen as a whole); the pyknic type, a larger proportion of "detail" answers (Enke [9]). Kretschmer explained the preponderance of kinesthetic answers in schizothymic persons as an expression of the tendency to an autistic transmutation of the environment such as characterizes schizophrenic psychotic behavior. He contrasts this subjectivity of the schizothymic, evidenced by the many "kinesthetic answers," with the objectivity and realism of the cyclothymic.

Reflex-like reactions in which preference is given either to form or to color, in experiments in which an alternative choice is possible, are apparently of great significance in the differentiation of psychologic traits of cyclothymic and schizothymic types. In the Rorschach test it is not possible to establish this reflex-like preference exactly, because the test itself necessarily involves "reflections, reproductions and attitudes." For this reason, the Rorschach test as applied to the investigation of Kretschmer's types has a limited use. More precise experimental methods are necessary. Scholl [10] has used tachistoscopic exposures of colored figures. His paper is a model of this type of experimental investigation, both in method and in interpretation of results. The subject to be tested is shown a colored form which he has to identify later in a group of similar forms which are tachistoscopically exposed to him. In this way it can be precisely determined whether his identifications are influenced more by color or by form. Scholl established by these experiments the interesting fact that cyclothymic types are more sensitive to color, and schizothymic types more sensitive to

9. Enke, W.: Die Konstitutionstypen im Rorschach'schen Experiment, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:645, 1927.

10. Scholl, R.: Die teilinhaltliche Beachtung von Form und Farbe und ihre typologische Bedeutung, Ztschr. f. Psychol. u. Physiol. d. Sinnesorg. **101**:285, 1927.

form. Kibler [11] and Enke [12] also found that the cyclothymic and schizothymic (or pyknic and leptosome, respectively) types differed in their sensitiveness to color as opposed to form.

A second phenomenon deduced from psychologic experiments is what Kretschmer calls "capacity to split" (Spaltungsfähigkeit). The whole conception of splitting, as here used, has of course a significant relationship to the clinical phenomena emphasized by Bleuler, on which the term schizophrenia is based; but when used in the sense of a psychology of comprehension and thinking, it is independent of clinical observations. Kretschmer goes so far as to say that one would speak of the psychologic constitution of the leptosome (asthenic) type as schizothymic even if there were no such mental disease as schizophrenia. In a test devised by Enke,[13] the subject has to put a piece of paper in an envelop. On this piece of paper are a number of squares of different colors. The squares of each color have to be counted while the piece of paper is being put into the envelop. Pyknic types take more time for this test and make more mistakes than asthenic types. In Kretschmer's terms, they are less able to split their whole consciousness into partial intentions. In another test of Enke [12] a long word is tachistoscopically exposed a number of times, each time so briefly that the subject cannot read it. Here also, the two types show opposing reactions. The cyclothymic personalities (corresponding to pyknic body types) have a tendency to guess at the whole word again and again in their attempt to identify it. The schizothymic types (corresponding to leptosome body types) isolate small fragments of the word at each exposure and try to combine them. Kretschmer speaks of the former as the synthetic type of comprehension; of the latter, as the analytic type of comprehension.

In view of the obvious comparison with the manic symptomatology, it is especially interesting that a greater "distractibility" can be demonstrated in normal cyclothymic subjects than in schizothymic types when they are tested by light signals interrupted by disturbing stimuli (van der Horst [3] and Kibler [11]). Pyknic types are more influenced by the disturbing stimuli, while schizothymic subjects "here again are able to split the course of impression into those elements which belong to the task and those which do not" (Kretschmer).

A further interesting psychologic phenomenon in which leptosomes and pyknic types seem to differ is the tendency to perseveration. Van

11. Kibler (footnote 5, second reference).

12. Enke, W.: Experimentalpsychologische Studien zur Konstitutionsforschung, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:770, 1928.

13. Enke, W., and Heising, L.: Experimenteller Beitrag zur Psychologie der „Aufmerksamkeitsspaltung" bei den Konstitutionstypen, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:634, 1929.

der Horst found this in his association experiments, and Enke in his tachistoscopic tests with the exposure of colored syllables to which the subject was asked to react first as to the color and then as to the content. Differences in perseveration are regarded by Pfahler [14] as the fundamental distinguishing feature in the experimental analysis of personality types. His conclusions are based on extensive and painstaking investigations with blot-picture interpretation tests, association experiments, special memory tests, etc. He distinguishes two patterns of behavior in the reception and elaboration of mental stimuli, namely, perseveration and association. He arrives at the postulation of two types, the "schizothymic type, with strong perseveration" and the "cyclothymic type, with weak perseveration." Pfahler's claim that the psychologic differences between these types can be clearly demonstrated even in children aged from 10 to 11 years would seem to deserve the most careful checking up by other psychologists.

Many investigations have undertaken to determine by tests the differences in psychomotor responses between Kretschmer's somatopsychic types. These researches seem to have been inaugurated by Russian authors.[15] So far the results of these attempts to distinguish types of motor behavior seem to be less convincing than the experiments previously outlined. Some Russian authors, however, as well as Liepmann [16] and Enke,[17] seem to have obtained suggestive and interesting results. The tendency of some Russian authors to develop neurologic hypotheses ("relative extrapyramidal insufficiency" of leptosome types [Jislin]) seems premature, although there are undoubtedly important relationships or transitions between the experimental psychologic investigations of psychomotor responses, including handwriting,

14. Pfahler, G.: System der Typenlehren. Grundlegung einer pädagogischen Typenlehre, Ztschr. f. Psychol., 1929, vol. 15.

15. Gurewitsch, M., and Oseretzky, N.: Zur Methodik der Untersuchung der motorischen Funktionen, Monatschr. f. Psychiat. u. Neurol. **59**:79, 1925. Oseretzky, N.: Die motorische Begabung und der Körperbau, Monatschr. f. Psychiat. u. Neurol. **58**:37, 1925. Gurewitsch, M.: Motorik, Körperbau und Charakter, Arch. f. Psychiat. **76**:521, 1926. Ssucharewa, G., and Ossipowa, S. W.: Materialen zur Erforschung der Korrelationen zwischen den Typen der Begabung und der Konstitution, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:489, 1926. Jislin, S. G.: Konstitution und Motorik, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:240, 1928.

16. Liepmann, W.: Psychomotorische Studien zur Konstitutionsforschung, Deutsche Ztschr. f. Nervenh. **102**:146, 1928. (A good brief account is given in Abraham, P.: Les recherches cinématographiques sur les tempéraments, Bull. de la Soc. des formes humaines **6**:496, 1928.)

17. Enke, W.: Experimentalpsychologische Studien zur Konstitutionsforschung (Psychomotorische Untersuchungen), Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:798, 1929.

and the finer neurologic analysis of motor symptoms in organic disorders. There is an already large literature devoted to the investigation of handwriting in different types.

It has been possible, by such methods as have been mentioned, to isolate a number of psychologic phenomena in which there seems to be a pronounced difference—statistically calculated—between cyclothymic (syntropic) and schizothymic (idiotropic) types. It seems possible to demonstrate by psychologic experiments fundamental differences between the two series: the schizothymic, the leptosome or the schizophrenic patient, on the one hand, and the cyclothymic, the pyknic and the manic-depressive patient, on the other. To this difference of psychologic reaction type between the two series corresponds a similarity in reaction type within each series. About 800 persons, both well and psychotic, have so far been examined in these various experiments. Kretschmer, combining the results of experimentation with general observations, comes to the following conclusion: the leptosomes are more intensive, abstract, analytic, persevering (with some erratic deviations), subjective and suppressed in their feelings; the pyknic types are more "extensive," objective, synthetic, changeable and naively emotional. The greatest contrast is between autism and realism, which can be reduced to more primary experimental factors.

It is well known that one of the first problems attacked when the methods of experimental psychology were introduced into psychopathology was the influence of pharmacologic agents on mental reactions (Kraepelin). These pharmacologic influences have recently also been studied for the problems of experimental type psychology. The drug mescal (peyote) causes a psychopathologic condition which today, after a series of clinical studies, is fairly well known. Beringer,[18] in his monograph on mescal intoxication, stated that he could not find any differences in the action of the drug which might be definitely ascribed to specific personality types. In a recent study of seventeen persons, however, Bensheim[19] devotes especial attention to this problem. He has found certain typologic differences which seem to be significant and deserve careful checking by other observers, although he has unfortunately published his observations in a summary fashion, without giving complete records. It is his opinion that a difference does exist in the contents of the mescal-produced optic phenomena of the two types. The cyclothymic types tend more to ornamental pictures—colors and forms continually changing and replacing each other—with only a few individual plastic figures. In the visions of schizothymic subjects, on the other hand, figures predominate. They also change and form ever new

18. Beringer, K.: Der Meskalinrausch, Berlin, Julius Springer, 1927.

19. Bensheim, H.: Typenunterschiede bei Meskalinversuchen, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:531, 1929.

combinations: mountains, castles, heads of animals and men. Schizothymic types have a stronger tendency to uniform stereotyped series than cyclothymic subjects. The mood of the latter varies from euphoria to depression—they establish closer contact with their surroundings. The former, on the contrary, feel themselves "shut in" with their visions and experiences, and may even assume ecstatic attitudes. The cyclothymic subject shows more associative tendencies; the schizothymic, more perseverative tendencies. The former remains near to reality, and his visions seem to be largely "illustrations"; the latter has a tendency to experience a "cosmic unity" and to visualize a concrete picture in place of an abstract thought which cannot be formulated. Great reserve is indicated with regard to Bensheim's conclusions. One gets the impression that the typologic conceptions of Gaupp's clinic and Kroh's laboratory, both at Tübingen, have colored his observations a good deal. But even with this reservation, his observations deserve careful attention.

Those who are still swayed by the period of stagnation of experimental psychologic methods in psychiatry will be doubtful as to the results of this new development of experimental type psychology. But the work already done constitutes only a beginning, and it would seem that it opens up a field for investigation which promises further interesting results.

Abstracts from Current Literature

THE DIAGNOSIS OF SUPRASELLAR TUMORS, ESPECIALLY TUMORS OF RATHKE'S POUCH. (From a report made at the XIII International Congress of Ophthalmology.) LUDO VAN BOGAERT, Rev. d'oto-neuro-opht. **7**:645 (Nov.) 1929.

The embryologic development of the hypophysis is described, showing the complexity of the evolution. From the buccal cavity of the embryo, a fold (the future adenohypophysis) extends toward the cerebral vesicle, eventually becoming separated from the stomodeum. This is met by a downward extension from the cerebral vesicle (the infundibular process), the two eventually forming the hypophyseal rudiment, which comprises two zones: an adenohypophysis and a neurohypophysis. The remains of the pharyngohypophyseal canal are found in the cartilaginous rudiment of the sphenoid or, very exceptionally, as an accessory hypophysis of the palate. The infundibular process is found finally in the form of two residual nests, the one above, the other below the rudiment of the sellar diaphragm.

These embryonal rests offer an excellent opportunity for the development by embryonal inclusion of tumors and they may be arranged in five groups: 1. a superior epithelial group on the supero-anterior face of the infundibular stalk; 2. an inferior epithelial group located at the insertion of the stalk in the pituitary gland; 3. the parahypophyseal group of Dandy and Goetsch, corresponding to the cranial accessory hypophysis of Arai; 4. the intrasphenoidal group, corresponding to the craniopharyngeal accessory hypophysis of Arai; 5. the pharyngeal accessory hypophysis of Arai.

Besides these, there are found in the vicinity of the sella turcica the residue of the notochord causing osseous tumors; tumors of embryonal origin comprising teratomas, dermoid cysts; neurohypophyseal dystopias; certain cerebral cholesteatomas and tumors of the chiasm due to defective embryonal development.

The suprasellar region, lying between the chiasm in front, the cerebral peduncles behind, the sellar diaphragm below and the floor of the third ventricle above, may harbor various neoplasms of which the common symptomatology depends solely on the organs affected by their growth. The optic chiasm, lying between the jaws of a pincers formed by the infundibular recess below and the optic recess of the third ventricle above, is most exposed to the influence of tumor growth.

The relation of the chiasm to the hypophysis and the hypophyseal stalk is variable; this and also the resistance of the sellar diaphragm determine the quickness of the appearance of chiasmal symptoms. The general localization of tumors of this region is easy, but differential and etiologic diagnosis is more difficult. The progress of neurosurgery is dependent on preoperative precise histopathologic diagnosis. Ophthalmologic examination and clinical and roentgenologic studies permit a differential diagnosis of the different varieties of suprasellar tumors. This report is limited to a neurologic and roentgenologic study of tumors of the pharyngohypophyseal pouch.

Careful perimetric examinations for white and colors are of the utmost importance and permit an early diagnosis at a time when the eyegrounds show no change. The relation of the tumor to the chiasm, the arrangement of the visual fibers and the point of beginning pressure will determine the perimetric modifications, degree and evolution of atrophy, its character, the presence or absence of early papillary stasis or a late edema. Hypophyseal tumors with suprasellar extension have the same perimetric characteristics as tumors of the pharyngohypophyseal pouch.

Tumors of the pharyngohypophyseal pouch developed from the inferior epithelial group compress the chiasm from below and in front, thus affecting the fibers from the superior temporal quadrant with conservation of the macular bundle.

Tumors developed from the superior epithelial group compress the chiasm from below and behind and are the most common. They affect the fibers from the inferior quadrant and cause central or paracentral scotomas.

The earliest symptom of the chiasmatic syndrome is a bitemporal quadrantic hemianopia for colors, while the temporal field still presents only a slight notch for white. As the lesion progresses, the temporal defect extends downward, affects the macula and causes, at times, a notch in the nasal field. The evolution can proceed in various ways but the end is always the same: complete bitemporal hemiachromatopia or hemianopia. These different forms of visual fields are classic, but one frequently meets bizarre scotomas for colors, islands of vision of variable forms, etc. Pallor of the disk, at first temporal, soon appears and resembles toxic atrophy, but the cupping is not so great. Homonymous hemianopias are also seen if the pressure is a little to the side. A more advanced stage is primary optic atrophy, seen in cases with subchiasmatic compression. In cases with suprachiasmatic compression (infundibular tumors) there is typical papillary stasis.

In regard to tumors, primarily subchiasmatic and extending to the third ventricle, Cushing is quoted: "In white atrophy even if there is considerable increase of intracranial pressure from internal hydrocephalus, choked disc will not be produced if there exists a local lesion which compresses the optic nerves and prevents the cerebrospinal fluid from accumulating in their sheaths." These classic appearances are not found always; sudden blindness without atrophy (hysterical), perimetric changes only for colors, horizontal hemianopia, binasal hemianopia (double tumors in the angles of the chiasm) are some of the variants.

In interstitial tumors (glioma) of the chiasm, the evolution is different. Vision is lost rapidly, atrophy on the two sides is dissociated and if hemianopia exists it is less typical.

Distant lesions may affect the chiasm. In meningiomas or endotheliomas of the orbital surface of the frontal lobe, one finds retrobulbar neuritis with central or cecocentral scotomas on the side of the lesion and papillary stasis with conservation of central vision in the opposite eye. Finally, on the side of the lesion there is only a small island of vision and eventually unilateral amaurosis with a pale, normal papilla or a late stasis. In the opposite eye the stasis is typical and is followed by secondary atrophy.

The neurologic clinical picture will depend on the point of origin of the tumor, the anatomic relations of the organs affected and the age at which they are affected. The most frequent suprasellar tumors are congenital tumors of the craniohypophyseal canal. They are especially tumors of the first two decades of life although they are also met in advanced age.

The first symptom is frequently the chiasmatic syndrome. The second organ affected is the hypophysis with its pituitary stalk. If the tumor arises in the upper epithelial group, it extends directly toward the floor of the third ventricle and the infundibulothalamic region is affected before or at the same time as the chiasm, the hypophyseal gland being protected against compression by its sellar diaphragm. The hypophysis and perhaps the infundibulohypophyseal region is intimately concerned with growth and sexual development during adolescence. If tumor of the hypophysis or the diencephalohypophyseal region appears during childhood or adolescence, one observes a syndrome of infantilism. Depending on the period of inception, the retardation of development will influence the whole organism or only the development of the genitals and the secondary sexual characters. In the adult there will be seen either a dyspituitarism with emaciation or the adipose syndrome. These patients have an endocrine aspect. If the tumor from the start grows toward the third ventricle, the infundibulotuberian or hypothalamic syndrome is in the foreground, the intraventricular evolution being preceded or accompanied by the syndrome of internal hydrocephalus.

The syndrome of infantilism is a somatic syndrome characterized by hypoplasia of the genital organs and the absence of secondary sexual characters in a person past the age of puberty. The hypophyseal or infundibulohypophyseal lesion, while modifying or arresting the genital development, inhibits the general

growth. Children or adolescents presenting the syndrome of infantilism have at times a thin emaciated aspect. The adiposogenital syndrome of Babinski-Froehlich, observed in a case of tumor of the pharyngeal pouch, was believed by Erdheim to be of cerebral origin. In children there are arrest of genital growth, absence of secondary sexual characters and deposits of fat in the abdomen, pelvis, shoulders, neck and breasts; in the adult, progressive impotence with atrophy of the genital organs and regression of the secondary sexual characters in men. In women, there is first amenorrhea, increase of weight and the disappearance of libido. This is accompanied at times by a regression of the whole feminine morphology. Obesity can exist alone without sexual modification. It is more exceptional to observe only genital insufficiency.

Cushing described "lean" dyspituitarism in 1922. These patients do not gain weight. On the contrary, the skin is thin, pale and wrinkled; crow's feet, peribuccal, nasal and frontal folds are marked. They are asthenic, apathetic, somnolent and have polyuria and trophic troubles of the extremities. The secondary sexual characters are preserved. The skin is marbled by a pigmented lacework or is bluish suggesting the reticular cyanosis seen in young girls with thyro-ovarian insufficiency. These zones of cyanosis are found on the external surface of the legs, most marked at the inferior third of the calf and ankles. Their morphology keeps its gracefulness; the hair is fine, silky and less abundant than normal. It is not rare to see the hair of the brows, axillae or pubes become white or disappear. This type of dyspituitarism can be present from the beginning or can succeed an adiposogenital syndrome.

In the infundibular syndrome diabetes insipidus is frequent, and disturbed metabolism of carbohydrates is one of the principal signs in the infundibulotuberian syndrome. In two cases, one patient had hyperglycemia and the other hypoglycemia, but glycosuria was not observed. The disturbed regulation of the chlorides in diabetes insipidus was studied, but there are few data on this subject. The most characteristic disturbance of sleep is narco-epilepsy which is quite different from the state of hebetude seen in cerebral tumors in that it is a transient somnolence, which commences suddenly, leaves impaired memory and intelligence and can be interrupted by a strong stimulus. Cushing attributed the extreme slowing of psychic activity, found in some cases, to a remote effect on the frontal and temporal lobes but the same condition is seen in tumors of the pharyngeal pouch and the infundibular region. Emotional disturbances are sometimes pronounced, even going on to hypomania. Confusional crises have been noted and amnesia is frequent. Weisenburg and Mott have reported cases with the aspect of dementia paralytica. The crises of narco-epilepsy are accompanied by confusional and psychosensorial disturbances. One sees a curious mixture of amnesia and fabulation. Weisenburg reported sixteen cases of infundibular tumors with crises of excitation with somnolence.

Several cases with disturbance of heat regulation have been observed; in Cushing's case there was a rectal temperature of 94 F. In one of the author's cases of infundibular tumor with hypertension, the hypothermia yielded to lumbar puncture. These observations show that there is a heat regulating center in the infundibulotuberian region and that the thermic level is lowered by the paralytic phase and raised by the stage of excitation.

Cardiovascular disturbances, seen during operation on these tumors, are not always from toxic absorption, but from interference with the cardiovascular centers in the floor of the third ventricle by the operation. Death with lethargy, hyperthermia and total relaxation of the sphincters support this view. Disturbed respiration, even Cheyne-Stokes respiration, has been observed.

As the tumor grows, it can invade the third and the lateral ventricles, and produce an interpeduncular and then an intraventricular syndrome. The interpeduncular phase is marked by motor symptoms, due to compression of the foot of the peduncle and of the roots of the motor oculi in the optopeduncular space and to irritation or inhibition of the function of the red nucleus and the nearby

superior cerebellar peduncle. This latter causes the syndrome of rubric disequilibration.

As soon as the tumor reaches the third ventricle it affects successively the anterior pillar of the trigone, the capsule of the mamillary bodies, the optic tract, the foot of the cerebral peduncle, by which the pyramidal tract reaches the internal capsule, the lenticular bundle, the body of Luys, the anterior end of the locus niger, the central gray nucleus, and the intrathalamic relays of the red nucleus. Thus are produced pyramidal and extrapyramidal symptoms. To the former belong spasmodic paraplegia with abolition of all reflexes, except the plantar skin reflex, and simple flaccid paralysis of the legs. Among the latter are hypertonus of the legs, sometimes occurring in crises, slowness of movements, akinesia, cataleptic tendencies, slow speech, absence of facial expression and trembling. The author presented the first observation of an hypophyseal tumor with a parkinsonian and thalamic syndrome.

Sensory symptoms of the thalamic type were described by Weisenburg, who emphasized the existence of pains of central type with important vasomotor and trophic disturbances. These crises of pain resist all analgesics. Two verified cases showed marked destruction of the internal nucleus of the thalamus.

Cerebellar symptoms may lead to diagnostic errors. Bogaert and Martin, in 1928, reported two cases with a cerebellar syndrome, which caused an error in localization. In the first case there were titubation, unilateral deviation, hypertonia, astasia and ataxia; in the second there were added a pendular reflex, passivity of André Thomas, and asymmetry of segmental positions (Rossi).

. The observations of Bailey and the author reveal the following facts: 1. A minute anamnesis does not permit a sure decision between a suprasellar and a cerebellar localization. 2. The ophthalmoscopic aspect of suprasellar tumors can be lacking. Papillary stasis and secondary atrophy were found. 3. Erosion of the posterior clinoid processes may be found in cerebellar tumors. Small calcareous granules in the infundibular region may be present in the absence of tumor but important calcifications are pathognomonic of suprasellar tumors. 4. In order that the cerebellar symptoms may not lead to error, one must attach the greatest importance to the neurovegetative syndromes and infundibulohypophyseal dystrophies, especially if they exist before the late phase of hydrocephalus of the third ventricle.

In general, the cerebrospinal fluid shows a hyperalbuminosis, moderate lymphocytosis and only slightly increased pressure, although pleocytosis without meningitis has been noted.

The experience of neurologists and surgeons has proved that the roentgenogram alone does not have deciding value in the diagnosis. All cranial hypertension may cause hydrocephalus of the third ventricle and indirect alterations of the sella turcica, and cerebellar tumors can also cause osseous changes of the sellar floor. Intrasellar tumors cause enlargement of the whole sella. Any measurement of over 1.5 mm. in the vertical diameter and over 15.5 mm. in the horizontal diameter is considered abnormal. In the majority of cases the distention is at the expense of the floor. In consequence of special anatomic conditions, the intrasellar tumor may develop toward the infundibulum and exert pressure on the apophyses; then the distinction from suprasellar tumors is impossible. Suprasellar tumors, and especially those of the pharyngeal pouch, are localized near the base of the infundibulum and cause early hydrocephalus of the third ventricle, resulting in early enlargement of the sella and separation of the apophyses. The diagnosis may be difficult if the tumor arises from the inferior epithelial group of Erdheim and has an exclusively intrasellar development. A pathognomonic sign of tumors of the pouch of Rathke is the presence of spots of calcification above a sella turcica which is either enlarged or normal.

Ventriculography is particularly useful in distinguishing between suprasellar tumors with cerebellar signs and cerebellar tumors.

Hydrocephalus of the third ventricle can cause all the infundibulohypophyseal syndromes and roentgenologic signs of suprasellar tumors, but such observations

and verifications are few. They are infrequently caused by osseous tumors of the cranial base as well; and, in spite of extensive destruction of the sella, sphenoid and hypophysis, one sees no signs of hypopituitarism or hyperpituitarism. Hypertension is exceptional; papillary stasis is almost never present; the general state is good; the adiposogenital syndrome and polyuria are absent, and the chiasmatic syndrome is atypical. Besides, tumors of the base affect a different group of cranial nerves.

Suprasellar endotheliomas occur most often in persons between 35 and 50 years of age, do not cause nodular calcareous degeneration, and in general do not show roentgenologic changes other than erosion of the posterior clinoid processes. There is almost always primary optic atrophy on the side of the tumor and choked disk on the opposite side. Changes in adiposity, the hairy system, carbohydrate metabolism or sexual changes are exceptional.

Glioma of the chiasm is difficult to differentiate from tumors of the pharyngeal pouch since both are directly suprasellar. Primary optic atrophy is the same in both unless the lesion extends only to the insertion of the nerve. Quite late in the condition there is unilateral exophthalmus. The ocular signs progress less rapidly and the hemianopia is less typical than in tumors of the pouch. In advanced cases the sella is enlarged, but especially by distention of the optic foramina, and one never sees suprasellar calcareous shadows. When they attain a certain size, the tumors involve the stalk, and consequently there may be obesity and a slight polyuria, polydipsia and even somnolence, but never is there the characteristic adiposogenital syndrome. Both conditions are met with most frequently in children.

The differential diagnosis between suprasellar tumors and intrasellar tumors with hypopituitarism is important only in cases of adiposogenital syndrome or "lean" hypopituitarism in which one must distinguish between tumors of the pharyngeal pouch, chromophobe adenomas and adenomatous cysts. Tumors of the pharyngeal pouch never cause giantism or acromegaly; the adenomas are rare in the first two decades of life. The rule that adenoma with hypopituitarism belongs to adult life and that hypopituitarism in children almost always means a cyst of the craniopharyngeal pouch has few exceptions.

When the adenoma breaks through the sellar diaphragm and becomes suprasellar the differential diagnosis is difficult or impossible.

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THE ORGANIC SUBSTRATA OF NEURASTHENIA. A CONTRIBUTION TO THE STUDY OF THE PROBLEM OF NEUROSES IN GENERAL AND NEUROSES OF THE ORGANS. PART I. RUDOLPH KLOTZ, Ztschr. f. Kreislaufforsch. **21**:153 (March 15) 1929.

In part I, the author discusses the asthenic form of insufficiency of the middle lobe of the hypophysis. He first refers to a previous contribution by him in which he described venous capillary hyperemia in the region of the splanchnic system with the principal symptom of hypotension due to chronic circulatory asthenia. In this syndrome, Klotz expressed the belief that the hormone of the posterior lobe of the hypophysis is of causal significance. In the present contribution, he describes a condition whose substratum is a venous capillary hyperemia affecting smooth muscle cells in the sense of a hypotonia due to insufficiency of the posterior lobe of the hypophysis.

Of diagnostic importance in this syndrome are: (1) gastric symptoms (a sensation of weakness in the epigastric region, anorexia, a sensation of fulness and pressure in the stomach after meals, inability to take cold drinks, achlorhydria, noises in the stomach and a coated tongue); (2) intestinal symptoms (atonic obstinate constipation with putrid feces); (3) uterine symptoms (menorrhagia, especially during the climacterium when the ovaries begin to decline in function); (4) cardiovascular symptoms (palpitation and dyspnea after the slightest exertion, especially after eating, labile vascular tone without signs of cardiac

disease and hypotension with the accompanying weakness on effort). These circulatory disturbances give rise to various affective reactions with increased susceptibility to vagus irritation. The overloading of the internal organs with blood produces great pallor of the skin of the face and of the mucous membranes (although the blood picture and hemoglobin index remain normal), increased susceptibility of the skin to infections (herpes and parasitic skin diseases and persistent and annoying eczemas). These patients catch cold on the slightest exposure and have a tendency to rheumatism with retention of phosphates and urates. Owing to defective cell metabolism, the tissues become hyperacid. The body resistance to general infections is lowered with a resulting weakness of the defensive mechanism of the reticulo-endothelial system.

In addition to these somatic symptoms, there occur marked psychic changes, such as emotional changes at the slightest provocation, loss of the sense of well being, irritability and peevishness as well as loss of will power. These psychic changes are affected by periodic variations in the blood pressure, and are therefore most marked on arising in the morning and abate with the day's activity. In females the mental symptoms are worse during, before, and after the menstrual period, and they are markedly influenced in both sexes by seasonal changes, being more intense in the spring and fall.

As the disease becomes established, all symptoms lose their periodicity and become more or less continuous. The patients become exhausted mentally and physically, they become disinterested and remain inactive; a typical asthenia sets in, giving rise to the well known clinical picture of asthenic neurasthenia. The disease, according to Klotz, is not due to any primary cell disease, but is a secondary manifestation of a primary disturbance in the capillaries. While many of these cases are periodic, most of them are continuous and due to a chronic insufficiency of the hypophysis. As time goes on, new somatic symptoms appear that further incapacitate the patient. Diminished libido (impotence and frigidity) and various uterine malpositions, owing to loss of weight, are common, and the patients develop a diminished tolerance to alcohol, nicotine and narcotics. They are poor surgical risks because they take anesthetics badly, and because, owing to the capillary atony, they develop atony of the intestinal wall with failure of gas resorption leading to distention, intestinal paralysis and peritonitis. Owing to the sluggish circulation, these persons are also subject to postoperative thrombosis and embolism.

As a sequel to poor cerebral circulation, failure of the psychic faculties is common. The patients develop disturbances of memory, lack of inhibition, obsessions, anxiety, doubts and autosuggestibility; they become unusually sensitive to psychic and somatic stimuli and are conscious of their organs, which they describe as a feeling of tension, soreness and pressure.

The chronic form of insufficiency of the posterior lobe of the hypophysis may be summarized as a continuous asthenia combined with depression. Although the syndrome may occur in every kind of habitus, it is most common in the infantile-hypoplastic and in the tall eunuchoid types. Psychically, they belong to the psychasthenic constitution type.

Constitutional factors play an important rôle in this condition, which is due to a congenital defect in the function of the hypophysis with consequent debility of the smooth muscle cells. The principal function of the hypophysis is to supply the muscle cells of the blood vessels with substances capable of producing contraction of the vessel walls in order to maintain the blood pressure at a normal level, and to raise it above that level if the occasion demands it. (According to Biedl, extract of the posterior lobe of the hypophysis increases tonus and the contractile irritability of smooth muscle cells.) Insufficiency of this function may follow febrile infections (grip, pneumonia), increased mental and physical exertion, and such changes in the body chemistry as occur at puberty; overloading of the gastro-intestinal tract; alcoholism and the excessive use of tobacco are also causative agents.

Treatment consists in the employment of measures that tend to stimulate the function of the hypophysis. Of these, radiation (roentgen rays and diathermy), and the injection of hypophyseal extract are the most important. Myocardial tonics (caffeine), physical measures (exercise, baths, massage and deep abdominal breathing) are useful adjuvants as is well regulated psychotherapy (suggestion).

PART II. THE ERETHIC FORM OF INSUFFICIENCY OF THE POSTERIOR LOBE OF THE HYPOPHYSIS. Endokrinologie **4**:277 (Oct.) 1929.

When persons suffering from capillary atony (hypotension, physical and mental asthenia) are occasionally compelled by the stress and strain of life to make some extraordinary effort in order to maintain life, i. e., when they are compelled to perform functions which, owing to their marked asthenia, they are unable to do, the blood pressure rises. The first sequel to this rise in blood pressure is an increased activity of the heart (rapid pulse, cardiac palpitation, pulsations in the neck and functional systolic blows). This is folowed by great variations in the blood pressure (which is at first below normal and later continuously 150 systolic, or above); irregular respiration, scanning speech, dyspnea and a sensation of pressure and tightness in the chest. At the same time there appear insomnia, increased nervous tension and irritability. Psychic symptoms become a prominent feature and they are of the same nature as those described under the heading of asthenia, except for the absence of depression. The patients become vivacious, excitable, loud and impulsive and unable to adjust themselves.

The circulatory symptoms are easily recognizable as those of sympathicotonia. Sympathetic irritation alone, however, is not sufficient to explain the permanent hypertension. Owing to the diminution in the tone of the muscular coat of the vessel walls from the lack of muscle tone-producing hormone (derived from the posterior lobe of the hypophysis), there results capillary atony (venous splanchnic-capillary hyperemia). In capillary atony there occurs a fall in blood pressure and all symptoms of physical and psychic asthenia make their appearance. If the patient is now forcibly aroused from the lethargic asthenia and compelled to accomplish a "task" he can do so only with a rise in blood pressure. However, as the diseased cells of the muscular coat of the vessel respond to a contraction stimulus only, there results with every contraction a spasm of the capillary system which raises the blood pressure from subnormal, not only to normal, but beyond normal. In this manner every renewal of effort produces a new increase in pressure, so that these patients develop periods of hypotension which alternate with periods of hypertension. Although in the beginning only intense psychic stimuli, severe pains and excessive somatic irritations give rise to hypertonus, the persistence of such stimuli produces, as time goes on, a more or less constant hypertension. A characteristic feature in these persons is that they begin the day's work with all activities "slowed up," but as the day goes on they are unable, with their peculiarly labile psychosoma, to withstand any irritation without reacting immediately with hypertension. Such capillary spasm with consequent hypertension may be limited to an individual segment of the body; this would explain, in these patients, the frequent occurrence of migraine which can be readily relieved by treatment with solution of pituitary.

As the erethic form of insufficiency of the posterior lobe of the hypophysis, not unlike the asthenic form, is also due primarily to a relaxation of smooth muscle cell tonus, the treatment must also consist of the administration of hypophysis. In this connection Klotz recalls that he long ago called attention to the paradoxic fact that hypophyseal posterior lobe extract increases the blood pressure in those suffering from hypotension and diminishes it in those suffering from hypertension. In the erethic form, however, the drug must be given less actively to avoid higher variations in blood pressure. Treatment, therefore, with injections of posterior lobe extract must be avoided, at least in the beginning, and the tablets are to be preferred. Coffee, tea and tobacco as well as physical and

mental stress must be avoided. Of great benefit in these cases are: the administration of brombaldrian, and physical and mental rest as well as a change of occupation.

According to the author, the discussion of insufficiency of the posterior lobe of the hypophysis must also include another condition, that of vagus irritation. This syndrome is characterized by hyperacidity with symptoms of dyspepsia, nausea, vomiting, increased peristalsis and diarrhea (in some instances obstipation), urinary tenesums, and a tendency to uterine bleeding, endocervicitis and endometritis. This syndrome was formerly designated as "vagus neurosis," and its frequent association with pains and cramps in various organs led frequently to a wrong diagnosis of appendicitis, stone formation and cardiac disease. The symptoms referable to the stomach, intestines, bladder, uterus, heart and capillaries can be relieved by the administration of epinephrine, because they are due to a relaxation of the tone of the sympathetic and an overactivity of the vagus consequent to an insufficiency of the adrenal system. It is noteworthy that in some of these cases the blood pressure may also be moderately increased. As the sympathetic innervation becomes defective from an insufficiency of the chromaffin system, there also results a diminution of tonus in the cells of the muscular coat of the blood vessels. Owing to this there is frequently observed in these cases a venous hyperemia of the splanchnic capillary system which may produce capillary spasm with increased blood pressure. Most of the patients afflicted with this syndrome are of the pyknic apoplectic type and have a tendency to obesity, arthritis, cyclothymia and great stubbornness. The functional deficiency in the adrenal system may be latent. Many of the so-called "vagotonics" may be included in this group; their tendency to vagus irritation is due not to functional but to organic causes. To check the acute irritation phenomena atropine is given subcutaneously or by mouth (0.0005, Gm. three times a day); epinephrine may occasionally be employed for a prolonged period, and for this purpose Klotz prefers Merck's suprarenal tablets (one tablet from two to four times daily after meals).

The cases just described are not cases of pure hypophyseal disease; they represent an insufficiency of the hypophysis and of the adrenal system. There is a close relationship between the hypophyseal and adrenal systems, because in one respect both of these systems have a common task, which is that of stabilizing through hormonal action the tone of the blood vessels, and of maintaining the blood pressure at a constant normal level. A diminution in posterior lobe hormone gives rise to a vicarious hyperfunctioning of the adrenal system, a persistence of which may finally lead to exhaustion and produce a secondary defect in the activity of the chromaffin system. In these cases the symptoms of hypophyseal insufficiency are associated with symptoms of vagus irritation and of adrenal insufficiency. A combination of this type has a very deleterious effect on the entire organism. Here again, capillary atony is a prominent phenomenon and is generally present from birth. To this congenital atony there are, in the course of time, superadded enteroptosis, hypotonicity, disturbances of the skeletal musculature, tendency to fibrillary twitchings, local cramps and poor muscle function with tendency to prolapses and hernias and great reduction of weight, with a disappearance of the fatty pads. In a word, the picture is that of Stiller's asthenia universalis, which is an important component of so-called neurasthenia, and all of which is due to an insufficiency of the posterior lobe of the hypophysis and of the adrenals. The persons suffering from this condition belong on the psychic side to the psychasthenic constitution type, and on the physical side to the asthenic-infantile habitus. Although the condition is in most cases chronic, it may in some persons develop acutely following an injury to the hypophysis; or to the adrenals by overexertion; by abuse with alcohol and nicotine, or abuse of the sexual functions.

As the etiology of this condition has not been understood up to this time, many of these patients wandered from physician to physician and were even subjected to useless and repeated laparotomies. Today, with specific therapy,

many of these sufferers can be relieved and even cured. The greatest causative factor in all the cases is the atony of the capillaries, which owing to the work of O. Müller, can be demonstrated microscopically.

All cases of arterial hypertension without organic disease and due to constitutional factors have up to the present been designated as "genuine hypertension." Today one can take some of these cases out of this group and regard them as due to disturbances of the glands of internal secretion. Of these, the outstanding type are the erethic, due to insufficiency of the posterior lobe of the hypophysis, or to the latter plus adrenal insufficiency. In some of them, the thyroid and ovary may also be of etiologic significance. In this entire group of cases, a lowering of blood pressure may be obtained following the administration of hypophyseal or of epinephrine tablets, depending on which one of these is at fault. Early prophylactic organotherapy is important because the persistence of hypertension for years may eventually lead to irreparable damage of the capillary vessels, and thus produce a true arteriosclerosis.

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PHYSIOLOGY OF THE VESTIBULAR CENTERS. (EXPOSÉ OF THE EXPERIMENTAL WORK OF R. LEIDLER). ISAAC ALFANDARY, Rev. d'oto-neuro-opht. **7**:743 (Dec.) 1929.

The studies of the physiology of the vestibular centers made by Flourens, Ewald and others were directed especially to the peripheral vestibular apparatus. Experiments on the second and third neurons have been rather rare. The important researches of Högyes, in 1880, were ignored by scientists until 1911 when the reports were translated into German. The valuable researches of Leidler deserve to be better known, both on account of their intrinsic value and on account of the control experiments to which they have given rise. On the one hand these experiments bear on the relations of the vestibular pathways with the cerebellum and the cerebral hemispheres, and on the other on the different parts of the vestibular pathways in the brain stem. The more easily observed nystagmus has been more often studied than the labyrinthine muscular tonus.

For the study of the relations with the cerebellum and cerebrum, the technic consisted in ablations of fragments or of the whole of these organs; for the study of the brain stem, in the laying bare of the posterior fossa and then puncturing the floor of the fourth ventricle with a needle or a Graefe knife. The animals (rabbits) were fixed on a rotary table. They were very lightly anesthetized, often only at the beginning of the operation.

The results of the experiments on the brain stem were: (1) A hemorrhagic lesion of the arciform fibers (van Gehuchten maintained that lesions of the arciform fibers at any level cause a contralateral nystagmus; he proved that the vestibulomesencephalic pathway contains contralateral fibers exclusively) at the level of the most inferior part of Deiters' nucleus (the zone of Deiters' nucleus comprehends the descending vestibular nucleus, Deiters' nucleus and Bechterew's nucleus — all the vestibular nuclei except the triangular) is followed by a spontaneous horizontal nystagmus the rapid phase of which is toward the side of the lesion. If the lesion is wholly of the inferior part, there is often combined with this nystagmus a gyratory nystagmus the rapid phase of which is directed backward. When the lesion was strictly unilateral, Leidler could observe the curious phenomenon of a reversal of the nystagmus: from time to time during the first two days, the nystagmus changed its direction to the side opposite to the lesion. No explanation of this phenomenon was found, but one can imagine that other factors than the topography of the lesion intervene to determine the direction of the nystagmus. When the lesion was bilateral, but on one side more than the other, the effect was the same as if only the more injured side alone was punctured. (2) A lesion of the zone of Deiters' nucleus or the fibers which go out from it, accompanied by a lesion of the radicular fibers of the vestibular nerve, causes a spontaneous contralateral nystagmus. (3) If the lesion is higher

up but does not go beyond the appearance of the magnocellular nucleus of Deiters, one observes again a spontaneous nystagmus directed toward the injured side and, in addition, a conjugate deviation of the head and eyes toward the operated side. The deviation lasts longer than the nystagmus, and when the lesion is pronounced it does not disappear at all. (4) When the lesion is still higher and reaches the knee of the facial or even the zone of appearance of Bechterew's nucleus, one obtains a contralateral nystagmus and also a vertical deviation of the eyes and an inclination of the head toward the side operated on. (5) If the lesion is above the nucleus of the sixth nerve, there is a spontaneous vertical nystagmus with often a gyratory component the rapid phase of which is directed forward. (6) Complete destruction of the radicular fibers of the vestibular nerve abolishes completely and definitely the caloric reaction on that side and incompletely and temporarily the rotatory reaction. (7) If the vestibular nerve is intact, a few arciform fibers suffice for the persistence of the caloric reaction. It is then, at the most, diminished. (8) If all the arciform fibers on one side and the posterior longitudinal bundle of the same side were destroyed, the vestibular reactions were abolished on both sides. (9) Destruction of the ventrocaudal nucleus of Deiters (the highest part of the descending nucleus) caused the same phenomena as section of the vestibular nerve except the instrumental reactions. (10) Lesions of Bechterew's nucleus and of the triangular nucleus do not influence nystagmus. (11) The symptoms provoked experimentally disappeared at the end of a greater or less time. The length of their persistence depended on the extent of the lesion.

To resume: (1) The direction of the nystagmus varies according to the height of the lesion, in that the low lesions cause a homolateral, the middle or high lesions a contralateral nystagmus. (2) The kind of nystagmus likewise varies according to the height of the lesion: the low lesions cause gyratory, the middle lesions a horizontal and the high lesions a vertical nystagmus. (These conclusions are put in question by the work of van Gehuchten and of de No.)

Of course, control experiments are necessary before drawing conclusions. Especially should one be prudent in applying to man the results obtained in experiments on rabbits. It must be remembered that the eyes of the rabbit are lateral and, consequently, that the various kinds of deviations and nystagmus have not their equivalents in man; that nystagmus in man is always bilateral and in the rabbit it is always unilateral. However, several of the observations in the experiments on rabbits have been noted in man. Thus, Marburg found a vertical nystagmus in a case of cysticercus of the fourth ventricle, which was of limited area and situated high up in the floor. Several observers have noted variation in the form of the nystagmus in man according to the height (of the lesion), agreeing with Leidler's experimental observations. A variation of the direction of nystagmus according to the height of the lesion has not yet been found in man except perhaps in certain cases of Wallenberg's syndrome.

However, Professor Barré and the author published a similar case in 1928 in which a spontaneous contralateral nystagmus was present. The lesion in this case was low, extending from the pinniform decussation to the superior third of the olive, and was situated in the gray reticulated substance, encroaching slightly on the olive, the lateral fasciculi of the bulb, the restiform body and the spinal root of the trigeminus and its nucleus. Perhaps not only the height of the lesion should be taken into account but also its nature. According to Marburg, irritative lesions of the zone of Deiters' nucleus cause a homolateral nystagmus; destructive lesions, a contralateral nystagmus. In any event, the phenomenon of a reversal of nystagmus, although it has been observed but once, proves that other factors intervene to determine the direction of nystagmus.

From the results of these experiments it was found that the centers for rotation, for deviation and for inclination of the head were also echelonned from below upward in the brain stem, when the word center is used in its widest sense. This applies also to deviation of the gaze. Bilateral lesions manifest themselves by unilateral disturbances, corresponding to the side most involved. This has been observed by Barré in man in syringobulbia. The conservation of a small

number of arciform fibers suffices for the persistence of the caloric reaction, at most diminished. This explains the fact that in lateral localizations of pontobulbar infiltrations the complete cerebellopontile angle syndrome is observed, except that the caloric reaction is normal.

These experiments do not explain the rôle of the triangular and angular nuclei (Bechterew).

Researches on the functional relations of the vestibular apparatus with the cerebellum give the following results: (1) When the cortex of the vermis was removed without disturbing the central nuclei, no spontaneous nystagmus was produced and no modification of the nystagmus reactions during and after rotation occurred. (2) When the vermis was totally removed, no spontaneous nystagmus was observed but the nystagmus produced by rotation was modified: during the first days following the operation one observed, on stopping the turning table, a nystagmus toward the direction of rotation in place of opposite this direction as is the rule. This is the "phenomenon of persistence of the perrotatory nystagmus." After some seconds this perrotatory nystagmus ceases and then reverses to the opposite side (postrotatory). (3) The postrotatory nystagmus was so rapid that it became impossible to distinguish the slow from the quick phase. It is "the oscillatory nystagmus" noticed by Bárány in tumors of the posterior fossa. (4) Sometimes, but not always, there is observed after cessation of the postrotatory nystagmus the appearance of nystagmus with the same direction as the perrotatory nystagmus (the Nachnachnystagmus of Bárány). (5) The extirpation of half of the vermis caused vestibular hyperexcitability on the side of the lesion only. (6) The ablation of a cerebellar hemisphere was without any influence on nystagmus, spontaneous or provoked.

A lesion of the cerebellum, whatever its extent or localization, never produces spontaneous nystagmus. This observation of Bauer and Leidler is in perfect agreement with those of Risien Russell and Munch, Ferrier and Turner, and others. Barré, in France, and Marburg, in Vienna, have supported it by clinical reasons and it seems to be admitted by the majority of neurologists and physiologists. If, at times, experimenters have noted a nystagmus following operation on the cerebellum, it can be asked if there did not occur an accidental hemorrhage in the vestibular centers, a thing difficult to avoid in these operations.

Late researches by the Viennese school have shown that if the cerebellum seems incapable of provoking a spontaneous nystagmus when the vestibular apparatus is intact, it intervenes to modify its direction when the latter is injured. This phenomenon must be compared with the dysharmonious vestibular syndrome noted by Barré in cases of lesion of the cerebellum. Finally, the experiments of Bauer and Leidler show that the cerebellum exercises an inhibitory action on the vestibular apparatus. Ths function is invested exclusively in the central nuclei of the cerebellum. The rôle of the hemispheres in the vestibular functions is not explained by their experiments.

The relation of the vestibular apparatus with the cerebral hemispheres has been little studied. Clinically, Dana and Mills have expressed the hypothesis, supported by anatomoclinical facts, that the cortical vestibular center is found at the level of the second temporal convolution. Cushing seems to be of the same opinion, while Weisenburg thinks that the relations of the vestibular apparatus with the superior centers are by the intermediary of the cerebellum and the red nucleus. Bauer and Leidler have studied this question by experimental researches with the following results: (1) Ablation of the cerebral hemispheres and of the thalamus does not influence nystagmus. (2) Ablation of one cerebral hemisphere produces a homolateral hypo-excitation and a contralateral hyperexcitation. Kleyn and Dusser have made control experiments on this point and have not been able to confirm the antagonistic action of the two hemispheres.

The first conclusion, if it is confirmed and if everything operates in man as in the rabbit, speaks against the hypothesis of Rosenfeld, Bartels and others of the cortical origin of the rapid phase of nystagmus. The disappearance of the rapid phase during narcosis, as observed by Rosenfeld, occurs only after the

corneal reflex has been abolished, i. e., when the bulbar centers are already affected, as Bauer and Leidler noted. A similar reflexion is applicable, according to the same authors, to the disappearance of the rapid phase during profound sleep in the new-born infant, observed by Alexander and Bartels in premature infants. However, Rosenfeld and then Barré and Metzger have observed disappearance of the rapid phase of provoked nystagmus during coma from softening or cerebral hemorrhage. These facts are difficult to explain if the interpretation of Bauer and Leidler is the only possible one. Numerous theories have been propounded to explain this rapid phase. According to Bauer and Leidler, the two movements have their centers in the vestibular nuclei but not at the same spot. These two centers (tonic and clonic) are phylogenetically different: the clonic, the younger, is less resistant to harmful agents.

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SUGAR AND CHLORIDE IN THE CEREBROSPINAL FLUID AND THEIR CLINICAL SIGNIFICANCE. S. N. SCHARAWSKY and A. B. MANDELBOIM, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:123, 1929.

The sugar content of the cerebrospinal fluid is one and a half times less than that of the blood, while the chloride content is almost one and a half times more (from 720 to 740 mg. per cubic centimeter compared with from 570 to 620 mg. in the blood). The chloride difference can be explained on the low colloid content of the fluid, but there is no explanation that is satisfactory for the lower sugar.

The reduction of sugar in acute bacterial processes is probably due to a glycolytic ferment liberated by the organisms, as this reduction is not observed in nonbacterial diseases or even in sterile purulent meningitis. The increase in cell count alone does not produce a glycolyse as some authors claim. Occasionally tumor cells produce a glycolyse, but mainly it is called forth by bacteria, which at the same time cause a reduction of p_H (from 7.55 to 7.1). Increase in the fluid sugar follows an increase in the blood sugar, e. g., in diabetes, tumor of the brain, epidemic encephalitis, dementia paralytica, etc.

Reduction in chlorides is caused by increased permeability of the plexomeningeal system and occurs in inflammatory conditions. Several animal experiments conducted by various authors are reviewed. Summarizing these works, it would appear that the fluid sugar follows the blood sugar rather tardily and without complete parallelism; the sugar content of the ventricle and cistern fluid is higher than the spinal fluid, and with the patient at rest and in a fasting state the chloride content of ventricle, cisternal and spinal fluid is equal.

In their research the authors collected 104 specimens from 101 patients. The fluid was withdrawn three hours after breakfast by ordinary lumbar puncture. In each case the fluid was also examined for gold reaction, globulin, cell count, Pandy, Nonne-Apelt, and Wassermann reactions, and a complete table of the observations is given. The sugar determination was made by the methods of Folin and Wu, Mandel and Stendel, Polonowsky and Duhot, Bang, Benedikt-Osterberg, and the microchemical method of Hagedorn-Jensen. The tests were made on the same day on which the fluid was obtained.

In eight cases of serous meningitis the sugar was normal in two, lowered in one and increased in the rest. In four cases of cerebrospinal epidemic meningitis, in which meningococci were present, the sugar was markedly lowered, being entirely absent in one severe case. In five cases of tuberculous meningitis, the sugar content was lowered. In edemas of the brain and tumors of the hypophysis, three cases out of eleven showed an increased, four a decreased, and four a normal sugar content. In nine cases of disseminated sclerosis, three showed normal, one increased and five cases decreased sugar content.

Twenty-five cases of syphilis of the central nervous system were examined. Cases of congenital syphilis, tabes, and dementia paralytica showed no change in sugar content. In six cases of syphilis of the brain two showed an increase, two a decrease, and two were normal. One case of cerebrospinal syphilis showed a

marked decrease. In pachymeningitis cervicalis syphilitica the sugar was normal in two cases. One case of meningomyelitis showed a slight increase, another a decrease. Of the twenty-five, seven showed a decrease, three an increase, and the rest wavered about the normal sugar content.

Of five cases of epidemic encephalitis, three showed an increase and two a decrease of sugar. Three cases of postinfluenzal encephalitis showed no change. In one case of malarial encephalitis the sugar was reduced. Two cases of myelitis showed a decrease; one patient with hematomyelia showed a decrease, and in one case of compressio medullae spinalis there was no deviation from the normal demonstrable. Two cases of epilepsy showed a decrease in sugar content. One case of jacksonian epilepsy showed no change. In cases of peripheral inflammatory disease (radiculitis and neuritis) there was no change. In five cases of endocrine disturbance the amount of sugar was normal; eleven cases of functional neuroses presented entirely normal results.

The chloride determination was by the modified method of Ban. Serous meningitis showed four with normal and four with decreased content. All the cases of epidemic cerebrospinal meningitis showed markedly decreased chloride. The same was true in four cases of tuberculous meningitis. Of nine cases of tumor of the brain, five showed decreased chloride content and the rest were normal. In one case of tumor of the spine there was a reduction. In six cases of disseminated sclerosis, two showed an increase, one a decrease, and the remainder a normal content.

In the group of syphilitic diseases, cases of tabes, dementia paralytica and congenital syphilis were normal in chlorides. One case of syphilitic meningomyelitis and one of latent syphilis showed reduced chlorides. No increase of chlorides was noted in any of the cases, and eight of the total of nineteen showed reductions.

In the acute as well as chronic cases of epidemic encephalitis there was no demonstrable change. In one case of severe malarial meningitis there was a reduction and also a slight reduction in a case of meningomyelitis. Three cases of epilepsy and one of Huntington's chorea showed no deviation from the normal. Cases of peripheral disease of the nervous system, endocrine disturbances and functional neuroses showed normal chloride content. Of nineteen cases in this group only two (disturbed endocrines) showed a decrease.

From the results only one constant picture presents itself, namely, in acute meningitis where there was considerable reduction in sugar content. Outside of this there was a fairly regular increase of sugar in encephalitis, epilepsy and in some of the brain swellings. In all other diseases the results were variable. The reduction in sugar was noted in cases with irritation of the meninges, e. g., in tabes, tuberculosis, meningitis or brain swellings. On the other hand, increases occurred with lesions of the brain substance, e. g., encephalitis, epilepsy and tumors of the brain. The authors believe that the amount of sugar in the spinal fluid depends much more on the underlying pathologic process than on the clinical form of disease. Frequently the sugar content can indicate the location of pathology (meninges or brain) and its nature, inflammatory (bacterial meningitis) or chronic granulomatous process (tabes).

An investigation of the sugar content can be of service in the differential diagnosis of the various forms of acute meningitis. Changes of the sugar during the course of the disease can also be of prognostic importance. The authors could not demonstrate any definite parallelism between the sugar content and the other serologic reactions. No relationship could be determined between the sugar and the pressure in the subarachnoid spaces. The normal sugar content they found to be from 50 to 53 mg. per hundred cubic centimeters, and the fluid sugar: blood sugar ratio to be 0.55:1. In acute meningitis this fell to 44.7 per cent, and in encephalitis it rose to 76.4 per cent.

The normal chloride content was from 0.72 to 0.74 per cent. The chloride determination was of less diagnostic value than the sugar. A noticeable and constant reduction was found in all cases of epidemic and tuberculous meningitis. Cases of

epilepsy, encephalitis and peripheral diseases showed normal chlorides. Of all the cases, only four showed an increased chloride content and two of these were multiple sclerosis, which usually shows normal or lowered chlorides. No relationship exists between the chloride content and the subarachnoid pressure. The concentration of protein affects the chlorides, the latter decreasing as the proteins increase and vice versa. In twenty-eight cases of lowered chlorides, twenty-two showed increased globulin and the remaining six were normal.

Sugar determination in the fluid therefore deserved more attention clinically than it is usually given, while chloride determination is not of so much value.

ALPERS, Philadelphia.

REGARDING CRANIAL HYPERTENSION: TRANSIENT AMELIORATION OF VISION BY INTRACAROTID INJECTIONS OF SODIUM IODIDE IN A CASE OF CEREBRAL TUMOR. EGAS MONIZ, AMANDIO PINTO and ALMEIDA LIMA, Rev. d'oto-neuro-opht. **7**:427 (June) 1929.

In a considerable number of cases of cranial hypertension, in which arterial encephalography had been practiced, amelioration of the syndrome of hypertension by the use of intracarotid injections of sodium iodide was seen. When the relief was marked and lasting, the cases were probably encysted serous meningitides. In cases of cerebral tumor, the results are not positive, but even here important relief of headache or vision is often noted. This action is not easy to explain because the etiology of cranial hypertension is not clear. Neither the size nor the location of the tumor fully explains the mechanism of hypertension. Recently, a patient was seen with a very small tumor of the frontal lobe which rapidly caused amaurosis and violent headache without ventricular dilatation; on the other hand, another patient with a large tumor of the corpus callosum and of one of the frontal lobes showed no definite symptoms of hypertension. Rapid growth of the tumor tends to increase tension, but the growth can appear to be rapid when inflammatory processes intervene. A tumor of slow growth can produce no appreciable symptoms, but at any moment signs of increased pressure (choked disk, headache, vomiting and vertigo) may appear. In the majority of cases, the determining factor in the occurrence of cranial hypertension is an inflammation of the pia mater.

Papillary stasis can occur in other conditions — serous meningitis, ependymitis, traumatism and subarachnoid hemorrhage, but the frequency is not the same in all.

The injection of iodide of sodium in the internal carotid acts by diminishing the inflammation of the pia mater and probably not by its hypotensor action, since the amount used, from 6 to 7 cc. of a 25 per cent solution, is not enough to produce a hypertonic fluid.

A patient, aged 18, began in December, 1928, to suffer with severe headaches, which were worse on the right side. There were vertigo, diplopia and diminished vision. The mother died of tuberculosis. The patient's past history was without significance. Examination revealed nothing abnormal except the following: triceps and radial reflexes were a little more lively on the left, patellar reflexes were lively and equal, Oppenheim's sign was positive on the left, the abdominal reflex was abolished on the right; vision was very low in the right eye and much diminished in the left, with bilateral optic neuritis.

An injection of 5.5 cc. of a solution of sodium iodide was made into the right internal carotid artery on February 4. This was followed by an epileptic crisis, starting on the right and becoming generalized. Ten days later, an injection of 5 cc. was made into the left internal carotid. This was followed by a generalized epileptic attack, which was more marked on the right side. Roentgenograms were made of both sides of the head. On the left side, the picture was normal. The carotid siphon was normal, and the sylvian group of vessels was in the usual place. On the right, the carotid presented the picture of a double siphon, and the sylvian group was elevated and followed an ascending pathway in the anterior half. A neoplasm in the anterior half of the temporal lobe could cause this dis-

placement of the sylvian group. A ventriculogram showed a compression of the right ventricle, agreeing with the cerebral arteriograph. After a second injection of sodium iodide, ten days later, into the right carotid, the diplopia disappeared, the vision in the left eye became normal and was 6/10 in the right eye; the headache disappeared. Three weeks later, the vision in the right eye was 1/5 and in the left eye 1/2.

A subtemporal decompression was done, and a puncture in the anterior third of the temporal lobe was made. On removing the needle, blood spurted out of the hole. The diagnosis of a vascular glioma was made. Convalescence was normal.

The case is of interest because of the therapeutic effect of the injection, although it was temporary. It is known that, in cases of cerebral tumor, the symptoms of cranial hypertension do not persist, although the mechanical cause, from the presence and development of the tumor, remains the same.

This crisis of hypertension must be due to an intercurrent state, certainly inflammatory, and the amelioration obtained from injections of iodide of sodium must be due to the effect of it on the inflammation. The iodide solution passes very quickly through the arteriovenous network derived from the carotid and its action on the pia and some of the nerve cells must be very prompt. For these reasons it is believed that the hypothesis of an inflammatory etiology of cranial hypertension is warranted, although anatomic confirmation has not yet been obtained. This hypothesis has the support of important clinical arguments.

DENNIS, Colorado Springs.

CEREBRAL AND SPINAL COMPLICATIONS DURING PREGNANCY AND THE PUERPERIUM. B. J. ALPERS and H. D. PALMER, J. Nerv. & Ment. Dis. **70**:465 (Nov.); 606 (Dec.) 1929.

The central nervous system, as well as other body systems, suffers during the strain of pregnancy. Hemiplegia, chorea, tetany, encephalitis, meningitis, multiple sclerosis, myelitis, Friedreich's ataxia and other pathologic conditions involving it have been reported. Hemiplegia, a relatively rare complication, is caused as in other conditions by hemorrhage, thrombosis and embolism, of which the most common is hemorrhage. It is curious that the patients are usually young women. Syphilis is relatively unimportant as a factor. Hemiplegias are also often associated with kidney disease or eclampsia and may be ushered in by convulsions. The basal ganglia and internal capsule are the favorite sites. Hemiplegias due to hemorrhage carry a poor prognosis and when recovery has occurred the next pregnancy usually causes a recurrence.

Cerebral thrombosis in pregnancy not only causes hemiplegia but owing to wider extension has produced convulsions and more general symptoms. It is often associated with thrombophlebitis in other large veins. Aphasia is often an accompaniment to hemorrhagic hemiplegia. Difficult to distinguish from the toxemia of pregnancy is tumor of the brain, for papilledema may occur in pregnancy without this condition. Encephalitis during pregnancy is not common, only about thirty-five cases having been reported in the literature. The question of interference is debatable, the concensus being in favor of interference only as a final measure. In only one case has the disease been reported as transmitted to the fetus. Twenty-one of the thirty-seven cases reported in the literature ended fatally. Twenty-one of the children survived. There seems to be little relation between the month of gestation in which the symptoms appeared and the mortality.

Chorea is a condition frequently reported and apparently attacks multiparae more often; it is usual in the first six months of pregnancy. As a viable child usually results, it is better to allow pregnancy to proceed. Winkelmann studied the brain in one fatal case and found degeneration of the ganglion cells most marked in the striatum. Some authors consider it a disease distinct from ordinary chorea, while others challenge this view. Many cases of chorea gravidarum reported in the old literature may well have been choreiform tics or functional neuroses based

on emotional maladjustment. Visual disturbances are relatively common in the gravid state and blindness, acute and transitory, is usually due to uremia. The pupils and fundi are usually normal in these states. Albuminuric retinitis shows no feature peculiar to pregnancy, but is apt to leave more lasting sequelae than amaurosis. According to Black, partial optic atrophy usually results. The latter condition rarely occurs by itself but has been reported by Knapp, Helzbach and Weigelin. Finlay and others studied the visual fields during pregnancy and noted restriction occurring commonly in the temporal area which they attribute to the normal hypertrophy of the pituitary gland compressing the optic chiasm. Other observers are inclined to regard the condition as functional. Myelitis as a complication may occur during pregnancy, post partum or during the puerperium. Few cases are reported with autopsy. It has recurred with succeeding pregnancies and has receded after birth or induction of labor. Hematomyelia is rare and scantily reported. Tumor of the spinal column, an accidental complication, is more common in the literature. The authors report the first known case of Friedreich's ataxia as a complication, and one case of papilledema with eclampsia, two cases of epidemic encephalitis and three cases of myelitis. A comprehensive bibliography covering the subject is appended.

HART, Greenwich, Conn.

THE PATHOGENESIS OF DECEREBRATION IN THE HUMAN. O. S. WALSCHONOK, Ztschr. f. d. ges. Neurol. u. Psychiat. **122**:348 (Nov.) 1929.

The study of decerebrate rigidity in man is a relatively new problem. Few cases have been investigated from a histologic standpoint. Walschonok reports the case of a child, aged 14, in whom a spastic paralysis of all four extremities developed during the course of a year, together with the involvement of the third, fourth and sixth cranial nerves. The muscles of the extremities showed marked rigidity, with plastic tonus; there was definite rigidity of the muscles of the back and neck and of those of the lower jaw, causing an opisthotonos and trismus. Finally, the limbs were held in a definite position: flexion of the left arm with pronation of the forearm, extension of the right arm and maximal extension of the lower extremities. Tonic neck and labyrinthine reflexes were present. Necropsy revealed a large tumor of the right cerebrum, extending from the frontal lobe to the pons. This tumor had destroyed the right lenticular nucleus, almost the entire caudate nucleus, the right optic thalamus, the right peduncle, the collicular region and the upper part of the pons. On the left side all these areas were grossly intact, but histologically there was destruction of cell elements in the nucleus ruber, substantia nigra and other nuclei. The large cells of the putamen and caudate were changed on the left side.

Sherrington discovered the phenomenon of decerebrate rigidity, producing it by section through the corpora quadrigemina. The work of Thiele, Cobb, Bazett and Penfield showed that the impulses causing extensor tonus come from centers situated in the medulla, namely, the vestibular nuclei. Spiegel and his co-workers, however, claimed that this is not the only source of muscle rigidity, but they believed that the large cell elements of the substantia reticularis of the medulla and pons should be considered partially responsible. These areas send their impulses by the reticulospinal fibers into the anterior horn cells. Rademaker believes that decerebrate rigidity is due to destruction of the red nucleus, Forel's decussation, or the rubrospinal tracts.

Clinical cases of extensor rigidity have been reported by Wilson and Rademaker. In a case of Wilson's a tumor of the mesencephalon was found. In a case of Holmes' a tumor of the dorsal part of the mesencephalon was found, and on histologic examination the pyramidal tracts were found to be sound, while the rubrospinal tracts were diseased. In a case of Walshe's the oral part of the red nucleus was destroyed, while severe cell changes were found in the caudal cell groups. The case of Weisenburg and Alpers is not mentioned. In this case a decerebrate rigidity in man following encephalitis revealed extensive changes in the substantia nigra and nucleus ruber. In the case of Walschonok all of the clinical signs of

a decerebrate rigidity were shown. Plastic tonus was present and tonic neck and labyrinthine reflexes were present. Walschonok attempts to determine the reflex arc for the neck reflexes, but he says that it is only possible to state that in man this arc lies somewhere between the pons and the nucleus ruber in the region of the corpora quadrigemina and the pes pedunculi. The center for the labyrinthine reflex is in the mesencephalon.

With regard to the posture assumed by the patient, Walschonok points out that the flexor contracture occurs in the limb in which both pyramidal and extrapyramidal tracts were destroyed, while extensor contracture was present when only the extrapyramidal tract was injured. He concludes, therefore, that injury of the extrapyramidal system causes extensor posture, while a co-injury of the pyramidal tract produces a predominance of flexor contraction.

ALPERS, Philadelphia.

MENINGITIS AND MENINGO-ENCEPHALITIS IN INFECTIOUS PAROTITIS. R. J. WEISSENBACH, G. BASCH and M. BASCH, Ann. de méd. **27**:5 (Jan.) 1930.

The most common form of meningeal involvement in combination with infectious parotitis is the following: Suddenly all the typical signs of meningitis develop in a child. Lumbar puncture shows a marked cellular reaction without micro-organisms. After a few days, usually after from three to six, swelling of the parotid glands settles the clinical diagnosis. The parotid is usually only mildly involved and the meningeal signs disappear after a period of from one to three weeks. In a second group of cases the infection with the unknown micro-organism produces a clinical picture that closely resembles epidemic encephalitis. Vomiting, spasmodic contractures, transitory hemiparesis and oculomotor paresis, combined with meningeal symptoms and a cellular spinal fluid, are reported. The swelling of the parotid again follows the meningo-encephalitis, and all the signs of disease disappear as rapidly as they came. In a third group of cases of meningo-encephalitis the parotid was not involved and the connection of the clinical symptoms with the virus of the parotitis could only be established indirectly by the discovery of typical cases of parotitis in the family or neighborhood of the patient. In some of these observations the region of the parotid was sensitive to pressure, without showing any fluctuation.

An attempt was made to establish an early diagnosis by a careful examination of the cerebrospinal fluid. Following are the characteristics which allow a differential diagnosis from epidemic, tuberculous and syphilitic meningitis: The fluid is clear and sterile. It is not xanthochromic and contains a large number of cells, in most cases more than 100 and up to 1,000 per cubic millimeter. As a rule there are only a few polymorphonuclear cells, most of the cells being lymphocytes (from 63 to 100 per cent). The albumin is only slightly increased; the maximum was 1.42 Gm. per liter. The sugar content is normal and the chlorides are somewhat diminished. The number of lymphocytes decreases from the maximum to normal within from four to five days.

The sudden onset in a healthy child, the absence of fibrin and the low content of albumin make an early differential diagnosis from tuberculous meningitis possible. Furthermore, in the latter the sugar content of the spinal fluid is always diminished. If parotitis meningitis occurs in an adult syphilitic meningitis must always be considered first in differential diagnosis. Negative reactions to the Bordet-Wassermann test and the benzoin test are indications against a syphilitic infection, and a differential count of the spinal fluid cells in the latter infection usually reveals more intact polymorphonuclear, large mononuclear and plasma cells than in parotitis. The differential diagnosis from epidemic meningitis is sometimes difficult and can be established only in the later stages of the disease or if an epidemic is present. Meningococcus and other infections of the meninges can be diagnosed by cultures of the fluid, which are sterile in the parotitis infection. If a clear fluid makes diagnosis difficult, the presence of fibrin, the increased albumin and the large number of altered polymorphonuclear cells will help one to recognize these forms.

The favorable prognosis in cases of parotitis meningitis makes an early diagnosis valuable and the rapid improvement makes therapeutic action unnecessary.

WEIL, Chicago.

THE SOCIAL ADJUSTMENT IN SCHIZOPHRENIA. S. A. SOKOLSKAYA, F. I. GREENSTEIN and V. MOSHINSKAYA, Rev. Psychiat., Neurol. & Reflexol. (Leningrad) **4**:208, 1929.

The study was undertaken by the three authors in their capacity of District Psychiatrists in Leningrad. As they did not have the assistance of psychiatric social workers, all the social investigations, as well as the clinical studies, were made by the authors. As the problem is complicated, the behavioristic approach was emphasized in the study. One hundred and fourteen patients, between the ages of 15 and 30, were studied; sixty-three were men and fifty-one were women. The social adaptability of the patients was studied before admission to the hospital and after they were discharged into the community. The patients came from all classes of the population, with a good sprinkling of college students. The authors emphasize what they call "the personal complex," which is apparent in the investigation of their patients. The patients belong to opposite extremes; they are either extremely rigid, narrow, persistent and dynamic, and take themselves extremely seriously, or else they are extremely sensitive, introverted and shut-in. The first group is much larger than the second. In more than 75 per cent of the cases one could detect the so-called schizoid personality traits as they are commonly understood in America. It is interesting to note that most of the patients preferred to remain within their family; very few of them took any active steps toward marriage. There was nothing unusual or striking in the sexual life of the patients. Most sexual experiences are of such a personal character that one cannot obtain any reliable objective data.

In the cases with an acute onset, there was an acute environmental stress, such as unemployment, economic stress, complications at work and difficult family situations. It is interesting that difficulty at the place of work was not usually the cause of the illness but was one of the symptoms of the disease. About 20 per cent of the patients had a vague insight that something was wrong with them, and, in one form or another, tried to compensate for the disease by making attempts to become more sociable, active and studious, and to engage in physical culture exercises, etc. The negative compensation expressed itself in a marked withdrawal from the environment. Of extreme importance is the type of work which the patient does before the onset of the illness; even that has certain traits which point to the future illness. Twenty-six per cent of the patients were discharged as "recovered" from the hospital and are doing well in the community. This is a much higher percentage than is encountered in European or American hospital experience. A similar study conducted at the psychiatric clinic of the Second Moscow State University on 574 schizophrenic patients showed that the complete disability was less than in epilepsy. About half of the schizophrenic patients were able to return to the community; but of these more than 70 per cent had remissions. The whole problem of the adjustment of the schizophrenic patient to the community depends on a large number of variable factors, such as the social level of the specific community, proper vocational guidance, psychotherapy and the emotional level of the patient. The authors emphasize the necessity for individual work with patients. More intensive studies of the community are urged by the author.

KASANIN, Boston.

THE ANATOMY, PHYSIOLOGY AND PATHOLOGY OF THE RED NUCLEUS. U. DE GIACOMO, Riv. di pat. nerv. **34**:749, 1930.

The genesis of rubral symptomatology in man is discussed by the author from anatomic, physiologic and clinical aspects. He describes the experimental work that has been done on cats and rabbits, but lays stress on the fact that data derived

from animal experimentation are only slightly applicable to conditions produced in man by lesions of the red nucleus. He calls especial attention to the frequency of a slight contralateral hypotonia following such lesions. Phylogenetically, the red nucleus represents a particular evolution of its histologic characteristics and of its connection with other centers of the neuraxis. In cats, and even more markedly in rabbits, the large cell element predominates, but in man almost the entire nucleus is formed of small cells. This is the reason why the results of animal experimentation are of such slight value when applied to human pathology. The physiologic significance of the large cell element in the red nucleus is at present a matter of controversy. Practically, however, its significance is of negligible interest, on account of the anatomic differences just mentioned. Experimental lesions at the site of the small cell area of the red nucleus give rise to the phenomenon of contralateral hypotonia. These results agree with the most recent data observed in human pathology; in fact, destruction of the red nucleus in man reveals itself clinically (in addition to the phenomena of cerebellar dysfunction) by slight hypotonia, also contralateral. Furthermore, an alternate paralysis of the oculomotor nerves is almost constant in rubral lesions.

In human pathology, when isolated diseases of the red nucleus occur, there is usually no trace of the hypertonic syndrome, as from decerebration. Up to the present time there exists no anatomicoclinical proof that rubral alterations in man are ever responsible for hypertonic states, while the condition produced is even less comparable to the experimental rigidity of Sherrington. As a matter of fact, in the majority of maladies characterized by hypertonia, including those of the extrapyramidal system, the red nucleus is usually found to be intact or only slightly affected.

From the physiopathologic point of view, the red nucleus may be considered as essentially a center for the transmission of cerebellar impulses, regulated by cortical, pallidal and thalamic influences. The origin of the slight contralateral hypotonia may be explained in two ways: (*a*) by attributing to the red nucleus a specific tonogenic function (contradicted by Rademaker), or (*b*) by considering the hypotonia an element of the hemicerebellar syndrome which, with the alternate paralysis of the oculomotor nerves, constitutes the characteristic clinical picture observed in unilateral destruction of the red nucleus.

VINCIGUERRA, Elizabeth, N. Y.

THE STRUCTURE OF GLIOMAS. T. USĀWA, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **31**:1, 1929.

For the proper interpretation of the significance of structural variations in this type of tumor several factors must be taken into consideration. Of great significance must be the site of origin of the tumor; the structure, for example, of a glioma of the cerebellum is entirely different from that of a glioma of the cerebrum, and similarly the structure of a glioma arising from the periphery differs greatly from one arising in the white matter.

Another factor to be considered is the development of the cellular elements of the tumor. In two of three cases examined by the author the cellular constituents were mature plasma cells, whereas in the third case, the cells, though appearing definitely immature, differed from glia cells as regards both the nucleus and the cell plasma; there were undoubted evidences of arrested development at a stage during which further development continued only quantitatively and not qualitatively. Special consideration must also be given to the fact that mature glia cells in a glioma may undergo changes corresponding to the functional potentialities of the cells, i. e., the cells in one case may constitute fibrillogenesis, while in another they may enter into the formation of a more durable cyst wall. Again, a glioma cell may, in the form of a plasma cell, assume the character of a phagocytic scavenger cell without ever reaching the terminal stage of that type of cell. A glioma cell may also assume the characteristics of a dysplastic glia cell—a change not due to the nature of the tumor but to secondary degenerative changes within the tumor itself.

Another factor is the condition of the blood vessels. Thus there may occur a proliferation of the cells of the wall of the vessel which may be partly endothelial and partly adventitial, giving rise to a homogeneous mass of a finely fibrillated structure which, when studied with connective tissue stains, leaves no doubt of its mesodermal origin. With these facts in mind one may be justified in offering the hypothesis that it is the growth energy in the tumor which affects the glia as well as the walls of the vessels unless one is inclined to attribute the changes in the latter to the stimulating effect of proliferating glia.

Finally, one additional factor must be emphasized and that is that in no case was there anything found that could be interpreted as evidence of infection. There was no question that in every case the growth was infiltrative in nature. Wherever glial reaction was observed in areas not immediately adjacent to the tumor itself such reaction was due to pressure of the tumor on the one hand, and to edema of tissues on the other.

KESCHNER, New York.

ARTERIOSCLEROTIC PARKINSONISM. MACDONALD CRITCHLEY, Brain **52**:23 (April) 1929.

A very complete account of arteriosclerotic parkinsonism is presented and the author draws attention to this syndrome as a frequent manifestation. Although cerebrovascular disease may give rise to a complete picture of paralysis agitans, incomplete forms are more common. All gradations occur, from the mildest degree of hypokinesis and hypertonus to forms which clinically are indistinguishable from the classic idiopathic Parkinson's disease. The cases can be grouped into five clinical types, but Critchley emphasizes that a sharp differentiation is not possible: (1) early cases characterized by some immobility of expression and short steppage gait; (2) cases forming part of a pseudobulbar syndrome; (3) cases associated with marked intellectual defect; (4) pyramidopallidal syndromes, and (5) cerebellopallidal syndromes.

Some points of distinction between the arteriosclerotic and idiopathic varieties follow. In the former, symptoms may commence suddenly, but an insidious onset is more typical. Progression is more rapid and may proceed by a series of abrupt exacerbations. Although the usual age of onset is about the same for both conditions, an unusually early or a very late age incidence suggests a vascular basis. In arteriopathic cases tremor is usually absent, the muscles feel firmer to the touch and the rigidity is often characterized by a tendency toward catatonia. Many of the patients show "bulbar" signs, with emotional instability and a more or less profound dementia. They may also present other cerebral defects, as apraxia or aphasia.

The pathologic changes vary greatly in character and diffuseness, but the essential features comprise lesions in the globus pallidus and to a lesser extent in the substantia nigra. These are directly consequent on vascular disease. Pallidal lesions must not be regarded as the sole responsible agents in the clinical manifestations, for changes at other levels can be demonstrated as contributing toward the rigidity. Thus, mental impairment, pyramidal disease, changes in peripheral nerves, in the muscles, tendons, joints, and the blood vessels of the limbs, may all play a rôle in producing the arteriosclerotic syndrome of parkinsonism.

An excellent review of the conceptions advanced as to the nature of catatonia and arteriosclerotic senile rigidity is included. The interrelationship of the two latter conditions is discussed in detail.

BECK, Buffalo, N. Y.

THE CENTRAL VISUAL PATHWAY. PETER C. KRONFELD, Arch. Ophth. **2**:709 (Dec.) 1929.

Kronfeld opens his paper with a review of the history of the exploration of the central visual pathway. Hugenin, in 1870, studying a case of tumor with autopsy, first suggested the localization of vision in the calcarine cortex; Hun, a decade later, suggested the correspondence between the lips of the calcarine cortex

and the margins of the retina. Then came Wilbrand, who, in 1890, pointed out the projection of the retina on the cortex and first suggested the bicerebral representation of the macula. The author then speaks of Monakow whose refusal to accept cortical centralization was an aberrant path in anatomic history. He concludes with an account of the confirmation of the present theories of the visual pathway by wounds in war. Kronfeld then discusses the methods of investigating, listing anatomic means, such as degeneration staining and embryologic study, experimental methods, such as those on animals, and clinical methods, such as the investigation of the results of wounds. The bulk of Kronfeld's paper, however, is devoted to a study of the details of the anatomy of the central visual pathway. He believes that the temporal crescent of the visual field is represented on the nasal side of the retina, then on the ventral portion of the geniculate body and finally at the rostral edge of the calcarine cortex. Similarly, the dorsal fibers of the external geniculate body, representing the nasal visual field, are projected on the caudal side of the cortex. The optic cortex is a specialization of the occipital cortex, this specialization occurring when the radiation projects inward to form the line of Gennari. Finally, Kronfeld concerns himself with the pathology of these pathways. He calls attention to the fact that the macula is often spared because of its bilateral representation. Owing to the complicated structure of the medullary lamella, asymmetric defects are possible and are so explained. Hemiachromatopia is explained on the basis of special defects in the second and third layers of the cortex. The problem of optic agnosia ("soul blindness") closes the paper, and is assigned to the left macular bundle, whether disturbed in the cortical projection or in the optic radiation. The right macular bundle learns to take over these functions after a time, thus accounting for recoveries from soul blindness.

DAVIDSON, Philadelphia.

EXPERIMENTAL STUDIES ON THE DEVELOPMENT OF THE EYE: II. THE EYE-FORMING POTENCIES OF THE MEDIAN PORTIONS OF THE URODELAN NEURAL PLATE (TRITON TENIATUS AND AMBLYSTOMA PUNCTATUM). HOWARD B. ADELMANN, J. Exper. Zool. **54**:291 (Oct. 5) 1929.

A small median circular disk or a median strip removed from the anterior end of the neural plate and implanted into the belly wall of a host of the same species may give rise to a single eye, symmetrically related to a more or less bilaterally symmetrical segment of the brain. The relations of eye and brain are sometimes similar to those often observed in cyclopia. In other cases the single eye may be more or less symmetrically related to a rudimentary platelet of brain tissue, or brain and eye may be unconnected. In other cases the eye developing from such an implant may show some traces of doubling. Such eyes may or may not be connected to a brain vesicle or a disk of nerve tissue. In some cases two small eyes may develop, one on either side of a brain vesicle to which they may be attached. The eyes developing from the median disk or strip are surprisingly large, in a few cases approaching in bulk the eye of the host. In the case of single eyes and in most cases of almost single eyes forming from the implants, no structure which can be interpreted as "chiasma" is present. In many cases the donor of the implanted tissue lived and possessed two eyes.

The prospective potency and the prospective significance of the implant are, no doubt, quite different. The facts indicate that there is present in the anterior end of the neural plate material possessing more or less generalized eye-forming potencies, any portion of which is capable of forming any part of the optic apparatus. These potencies are more or less diffusely localized, but confined to the anterior portion of the neural plate. A median piece, removed from its normal environment and thereby released from the repressive influences of surrounding parts, in some cases differentiates harmoniously in a strange environment into a single eye. In the normal course of development this same tissue would probably have had a different fate.

WYMAN, Boston.

CEREBROSPINAL FLUID EXAMINED BY ULTRA-VIOLET LIGHT. E. FRETSON SKINNER, J. Neurol. & Psychopath. **10**:97 (Oct.) 1929.

A method of spinal fluid examination is presented which is believed to have diagnostic possibilities in some neuropathologic conditions. The author repeatedly warns that he is not advocating a new diagnostic method. The procedure depends on spectroscopic photographs obtained by means of ultraviolet light. Normal spectra contain large numbers of clearly defined lines the wavelengths of which are known and can easily be identified. Wavelengths varying from 7,594 Angstrom units at the red end of the spectrum to 2,149 Angstrom units at the ultraviolet end of the band are identified. Absorption spectra are merely those in which certain of the waves are dampened or absorbed by some substance through which they pass. The best known examples are those of hemoglobin and its derivatives. The absorption occurring when ultraviolet light was passed through distilled water, physiologic solution of sodium chloride or spinal fluid was slight.

Dementia paralytica usually gives a characteristic spectrogram, with absorption of the rays below 2,961 units. In tabes the absorption is marked but not so complete. Skinner states that the most striking spectrogram occurs in fluids from tuberculous meningitis in which absorption up to a wavelength of 3,248 units was observed. A case is cited in brief which clinically and serologically was thought to be tuberculous meningitis, but spectroscopic examination revealed an incomplete absorption. It proved to be meningismus.

The author is of the opinion that neither the cells nor the protein is responsible for the changes. "The only definite statement possible is that absorption seems to take place in toxi-infection conditions and varies directly with the severity of this process; the nearer a fatal termination the more complete the absorption."

It is singular, however, that the type of case with most marked absorption necessarily has greater density due to the presence of cells and protein. Unfortunately, clinical case reports and spinal fluid determinations are lacking.

BECK, Buffalo.

NERVOUS DISTURBANCES IN ERYTHREMIA. KEN TAGA, Jahrb. f. Psychiat. u. Neurol. **46**:274, 1929.

A woman, aged 72, showed evidences of polyglobulism complicated with arteriosclerosis, carcinoma of the body of the uterus and peritoneum, and bilateral upper motor neuron hemiparesis. Anatomic examination revealed thromboses in the peripheral veins, but in the central nervous system there were found only relatively slight hemorrhages in the meninges, especially in the pia, diffuse cerebral edema and disseminated areas of softening (red softening) which had apparently been preceded by hemorrhages. There were definite endarteritic changes in the cerebral vessels. Some of the arteries were overfilled with blood, while others were practically empty. It was particularly noteworthy that the vessels situated within the areas of softening were least affected. The author comments on the unusual character of the anatomic observations in the brain and meninges in this case as compared with those reported in the literature on polycythemia. He suggests that the reason for these unusual observations may, perhaps, be sought in the fact that the polycythemia in this case was complicated by the presence of arteriosclerosis and carcinomatosis.

KESCHNER, New York.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, Dec. 19, 1929

DONALD J. MACPHERSON, M.D., *President, in the Chair*

SYRINGOMYELIA WITH SPINAL FLUID BLOCK: REPORT OF A CASE WITH THE PATHOLOGIC OBSERVATIONS. DR. CHARLES KUBIK.

The patient was studied during life by Dr. J. B. Ayer and Dr. W. J. Mixter, whose notes I have used. The rather unusual feature of a spinal fluid block is the chief interest in this case. Guillain and Bertrand recently reported a similar observation, but in their case the block was caused by a localized tumor, apparently a glioma, while the rest of the cord presented the usual picture of syringomyelia. In the case considered here there was a diffuse enlargement of the spinal cord due to distention of the syringomyelic cavity with fluid.

The patient, a man, aged 24, was first seen in November, 1928. His birth had been premature, at 8 months, but development appeared to have been normal. When he was 12, it was noticed that he had a curvature of the spine that gradually became more pronounced. About one year before he was first seen he began to have difficulty in walking; he stumbled at times and his legs felt numb. Weakness of the left hand had been observed for several months; the right was thought to be normal. He had never been aware of any sensory symptoms in the arms or upper part of the body. There had been some urgency and frequency of micturition.

The pupils were equal and reacted normally; there was no ptosis or inequality of the palpebral fissures; nystagmus was present on left lateral fixation. There was no sensory impairment of the face or other signs of bulbar disease. The arms were moderately spastic. There were wasting, weakness and fibrillary tremors of the supraspinati and infraspinati muscles of both sides. The left arm could be raised with difficulty only to a horizontal position; the left grip was weak, but there was no wasting of the small muscles of the hand. The forearms were small but were said to have been so since birth; their strength was normal on both sides, as was the grip of the right hand. The legs were spastic. The muscles of the calf and foot of the right leg were smaller than the corresponding groups on the left side. All of the tendon jerks were brisk. The abdominal reflexes were absent on both sides. There was a Babinski sign on the left; the right plantar reflex was equivocal. At that time there were no signs of sensory impairment in the arms or upper part of the body, but all forms of sensibility were impaired in the legs. A month later there was diminished sensibility to pain and temperature, with normal tactile sense, from the upper part of the neck to and including the sixth cervical segmental area. Lumbar puncture at the same time disclosed evidence of block. There was no rise in spinal fluid pressure on jugular compression. The fluid withdrawn had an albumin content of 80 mg. per one hundred cubic centimeters and was negative in other respects. The Wassermann reaction of the blood and other laboratory tests were negative.

Traction was applied with the purpose of correcting the deformity of the spine, and for a time there was slight improvement in the patient's symptoms. The arms became stronger and the spasticity of the legs and sensory impairment of the arms and legs diminished, but lumbar puncture performed three months later (March, 1929) showed that the block persisted. During the next two or three months the symptoms again progressed; bilateral nystagmus was noted; the weakness of the left arm and hand increased; some wasting could be seen in the muscles of the left hand, and the strength of the right hand became somewhat impaired.

The triceps and biceps jerks were less active. The spasticity of the legs increased, more on the left side. Sensory impairment assumed the form it had showed before.

In June, 1929, a cervical laminectomy was performed and a diffusely enlarged cord was found with a central cavity which was distended with clear fluid. An incision was made into the cavity and, with the escape of its contents, the cord collapsed. Examination of the fluid disclosed one cell and an albumin content of 37 mg. per hundred cubic centimeters.

Following the operation the patient was restless and difficult to manage. He stripped the dressings from his wound, a spinal fluid leak developed, meningitis followed, and he died twenty days later. Numerous lumbar punctures after the operation disclosed normal spinal fluid dynamics.

Postmortem examination was restricted to the spinal cord, of which only the portion between the midcervical region and the lumbosacral enlargement was obtained.

The subarachnoid space contained a purulent fibrinous exudate. The anterior spinal roots of the cervical and upper dorsal segments were diminished considerably in size. The cord had the form of a flattened tube, with a cavity at its center which appeared to be continuous through the whole length of the specimen. The cavity contained no pus; its wall, except for a slight granular roughening at the level of the incision in the cervical region, had a smooth, almost glistening surface.

Sections from the sixth cervical, seventh and tenth dorsal, and third lumbar segments were examined histologically. Situated in a general way between the dorsal and ventral horns, the cavity had a number of projections in various directions at different levels. In the middorsal region, just to the left of the anterior median fissure, it sent a branch forward almost to the pia; in the lower dorsal region it extended into the right posterior root zone; in the lumbar region there were long narrow extensions, reaching almost to the pia, between the posterior columns and in the posterior root zone on either side.

Ventral horn cells were seen at all these levels. They were fairly numerous even in the cervical and middorsal segments; in the lower dorsal segment, larger portions of the anterior horns were preserved; in the lumbar segment, the greater part of the left anterior horn remained but the right was almost entirely gone.

There were almost no commissural fibers at the levels that were examined, only a few situated anteriorly in the cervical segment and a somewhat larger number in the lower dorsal segment. There was considerable thinning of all the fiber tracts, with a relatively good condition in the posterior columns even in the cervical part, roughly a descending type of degeneration. Except for greater destruction of the right anterolateral column and of the right anterior horn of the lumbar region, there was little difference between the two sides.

Microscopic examination of the cavity showed that the greater part of its wall was made up of glia cells and fibrils which formed a zone of varying thickness around it. A considerable portion of its anterior wall, however, was lined with columnar cells. In the cervical region these cells were short or flat and arranged in a single layer. In the lumbar portion they were long and slender and many of them had taillike processes terminating in fibrils which stained like glia fibrils with phosphotungstic acid hemotoxylin. Among them were cells, tapered at both ends, that sent narrow protoplasmic prolongations to the lining membrane of the cavity, and fibrous processes in the opposite direction. External to the cells already mentioned there were spindle-shaped and bipolar cells with processes and a zone of glia fibrils and nuclei with, here and there, a rounded or bipolar cell. The nuclei of the glia cells, similar in appearance to those of the columnar cells, were round or oval, of a fairly uniform size and considerably larger than the glial nuclei of the surrounding nerve tissue.

These observations, which call to mind the embryonic development of neuroglia from the cells lining the neural canal, seem to indicate that the glial tissue surrounding the cavity originates from an ependymal type of cell, possibly a fetal remnant that has undergone something in the nature of neoplastic activity.

DISCUSSION

DR. J. B. AYER: We did not make the diagnosis of syringomyelia. I have never seen any other case with block.

FORCED DRAINAGE OF CEREBROSPINAL FLUID IN OPTIC NEURITIS. DR. VIRGIL CASTEN.

Kubie, in 1923, worked out the principle of "forced drainage" on animals. Working with dogs, he found that the lymphocytes in one case, for example, constituted 4 per cent of the first 0.5 cc. of spinal fluid withdrawn, while after "forced spinal fluid drainage" a differential cell count showed 80 per cent lymphocytes. Microscopic examination of preparations from the central nervous systems of these dogs showed that there had been a marked extrusion of the perivascular exudate of lymphocytes into the subarachnoid space. This led to the assumption that such a "washing out" of the inflammatory products from the perivascular spaces might carry toxic agents as well, and in that way favorably influence the course of infections of the central nervous system. Kubie's work has gone far enough to show that the method of "forced drainage" is a safe procedure; hypotonic fluids can be administered orally, subcutaneously or intravenously during lumbar puncture and will cause an abundant additional flow of cerebrospinal fluid without subjective distress, respiratory difficulties or diffuse swelling of the brain tissue.

The following cases were reported from the Neurological Clinic, Massachusetts General Hospital and the Ophthalmic Clinic of the Massachusetts Eye and Ear Infirmary.

CASE 1.—On June 10, 1929, an accountant, aged 59, came to the hospital complaining of acute blindness. He had neurosyphilis and was being treated with intravenous injections of tryparsamide. Following the second injection, a bilateral optic neuritis or a toxic amblyopia occurred and vision was reduced to light perception in both eyes; the fields showed a marked concentric contraction. The eighth nerves also were involved; one had to shout to make him hear. In view of a possible toxic action on the optic nerve, such as Birsch Hirschfeld has described in cases of atoxyl amblyopia, I proposed to do "forced drainage."

A lumbar puncture was done between the third and fourth lumbar vertebrae with the patient lying on the left side. The pressure and dynamics were normal; the total protein was 38; there were nine lymphocytes; the Wassermann test was positive with both blood and spinal fluid. One hundred and eighty cubic centimeters of clear colorless fluid was removed. Eighteen hours later the patient had vision of fingers at from 4 to 5 feet (121.92 to 152.40 cm.) in both eyes.

On the next day, he counted fingers at from 6 to 10 feet (182.8 to 304.8 cm.). On that afternoon another "forced drainage" was done, 190 cc. being removed. The total protein was 75; the Wassermann test was negative. A third drainage was done and 140 cc. withdrawn. The patient could read the large headlines of a newspaper on the third day. Vision improved rapidly. On the fifth day he was able to read newspaper print. In all, five "forced drainages" were done and 850 cc. of spinal fluid was removed. On June 20, vision at the eye clinic was 20/20 in both eyes. The fields were markedly contracted concentrically (only a 10 degree central field). Hearing also was very much improved.

When last seen, on November 19, vision was 20/15 + in both eyes. The fields were much improved (about a 30 degree central field); however, the disks showed considerable pallor in both eyes. Hearing was normal. The neurosyphilis was apparently well under control judging from serologic examinations. The patient was back at work.

We have done forced drainage in four other cases with the following results:

CASE 2.—A single woman, a waitress, aged 32, entered the eye clinic on Nov. 23, 1929, complaining of loss of vision in the left eye. This had been noticed accidentally when she closed the right eye. The left fundus showed 1.5 diopters of papilledema and marked atrophy. The right fields and fundus were

normal. Vision in the right eye was 20/15, in the left eye 0. Two days later, she returned and could only count fingers at from 2 to 3 feet with the right eye and had no vision in the left. X-ray examination of the skull and sinuses gave negative results.

A "forced drainage" was done. The pressure and dynamics were normal. The fluid contained 35 lymphocytes in the first 0.5 cc., and 60 lymphocytes in the last 0.5 cc.; 150 cc. of fluid was withdrawn in three hours. Vision immediately following this was 20/20 + in the right eye; the vision in the left was unchanged. On the next day, vision in the right eye was 20/15, in the left eye 0. The Wassermann reactions of the blood and spinal fluid were positive.

On December 17, vision in the right eye was still 20/15, and in the left still 0.

CASES 3 and 4.—These were cases of retrobulbar neuritis observed in a late stage. Both patients recognized fingers at 1 foot (30.48 cm.). Each was submitted to forced drainage, but without much improvement.

CASE 5.—A laborer, aged 40, complained of loss of vision for two weeks. He admitted drinking a great deal and was an inveterate smoker. Vision in the right eye was limited to counting fingers at from 8 to 10 feet; in the left it was 20/50. The fields showed an absolute central scotoma for color in both eyes; twenty-four hours later, vision was the same as at entrance. A "forced drainage" was then done and 125 cc. spinal fluid removed. The pressure and dynamics were normal, as were also the chemistry and the Wassermann reaction. Immediately after, vision on the right was 20/100 and on the left 20/40. On the following day, vision on the right was 20/50 and on the left 20/20. Roentgen examinations, the Wassermann reaction of the blood, and other laboratory tests were negative. On the fifth day the patient was discharged. Vision on the right was then 20/20—2, and on the left 20/20+4.

DISCUSSION

DR. HENRY VIETS: It was indeed striking to see the dramatic improvement in case 1. It must be admitted, however, that a similar improvement occasionally occurs without such treatment, and I have recently had such a case. The recovery was much slower, however.

DR. C. A. MACDONALD: Were accurate hearing tests done? Is the deafness to be ascribed to the disease or to the drug?

DR. L. WOLFF: Was any arsenic demonstrated in the fluid?

DR. DONALD GREGG: Does this procedure give rise to headache?

DR. TRACY PUTNAM: We have been using this procedure in a number of cases of multiple sclerosis at the Boston City Hospital. The results have been inconstant, but the most marked improvement has been in the visual acuity and fields, which have improved to some extent in every case treated in which they were defective. One must, however, be very skeptical of any new therapeutic procedure in diseases as erratic in their course as multiple sclerosis and optic neuritis.

DR. V. CASTEN: I saw the first patient recently; he still showed a slight bilateral pallor of the disks. Of course, only 2 per cent of patients treated with tryparsamide have permanent ocular damage. No elaborate tests were done. Deafness has been reported in tryparsamide poisoning. In reply to Dr. Gregg's question, this procedure causes no more headache than does ordinary lumbar puncture.

A STUDY OF OBJECTIVE SIGNS OF ANXIETY. DR. HALE POWERS.

In the diagnosis of functional neuroses one is too dependent on the history as given by the patients. Often one can only guess whether a neurosis is of psychic or of other origin. Often one can only guess whether a patient is suffering from anxiety or from fatigue, and one does not know which of two opposite forms of treatment to prescribe. If it is an anxiety neurosis, occupation should be

prescribed; if it is a fatigue neurosis, the patient obviously needs rest. Again, one may be uncertain as to whether a knee jerk is increased because of an organic or a functional condition. Usually one must guess whether or not he is dealing with a malingerer. Any objective signs that will aid in answering these questions should be sought for and utilized. It is important to recognize the element of anxiety in a case, not only because anxiety often confuses the clinical picture, but because it is capable of invalidating a basal metabolism test and even an electrocardiogram. It is important because one frequently sees hysterical people wearing braces for imaginary "lower back strain"; one sees neurotic people cowering through life under a wrong diagnosis of myocarditis made by an electrocardiogram, and unfortunately, one sees thyroidectomy performed when the metabolic rate has been increased only by an anxiety neurosis. Having been impressed with the frequent occurrence, during routine neurologic examination, of certain unconscious movements made by patients who were in a chronic state of anxiety, I undertook to keep a record of these signs in order to determine their usefulness in diagnosis. Notes on the presence or absence of the signs have been made on the records of nearly all of the examinations made in the past nine months; but there has been time to analyze only the last 273 case records for the purpose of this report. Of these, the majority are functional neuroses, but some psychoses and some miscellaneous neurologic material is included. There are many objective signs of anxiety, indicative of its ability to derange the functions of the nervous system at all levels, from the vegetative functions up to the intellectual activities. Anxiety has its effect on the circulatory system, on the tone of the muscles, on the voice, on the digestive organs and probably on the mechanism that constitutes the defense of the body against an invading organism. However, not all of the signs of anxiety, but only a small number of them, that may be observed during an ordinary neurologic examination will be discussed in this paper. They are, as it were, a by-product of the procedure. Hitherto they have usually gone to waste, but they may be made useful. Certain voluntary but unconscious movements constitute these signs. The patient is placed at ease in a chair, with both feet resting on the floor, the knees being at right angles. When the knee perk is elicited, if the body is jerked as well, it is indicative of anxiety. The jerking of the body is usually done by the erector spinae and the gluteal muscles, and the movement may be very slight. Sometimes one will observe contraction of the abdominal muscles, elevation of the shoulders or jerking of the head in extension or rotation. Movements of the body produced by an exaggerated knee jerk need not be confused with these movements because these movements are produced by other muscles. Anomalies of the knee jerk constitute another group of the signs of anxiety. These are the reduplicated knee jerk, the multiple knee jerk, the double or bilateral knee jerk, the delayed knee jerk, the reversed knee jerk, the inhibited knee jerk and thigh abduction or adduction. The reduplicated knee jerk is a second voluntary one, occurring shortly after the first. I have seen it in conscientious persons who were troubled by doubts. The multiple knee jerk occurs in the panicky type of persons. The double knee jerk consists in kicking with both feet when only one knee is tapped. The delayed knee jerk is a voluntary one that occurs sometimes when the real quadriceps reflex is inhibited. The reversed knee jerk is a flexion of the leg occurring when the quadriceps reflex is inhibited. It is an extreme defense reaction. Thigh abduction and adduction are usually slight movements. A description of this phenomenon was recently published by an observer who implied that they were associated with a lesion which he had not yet been able to localize. They are only one of the defense movements and are diagnostic only of anxiety. In many cases tapping the spine with the hammer will induce a body jerk, a head jerk or abduction or adduction of the thighs. For convenience, I have referred to one or more of these defense movements as an anxiety reaction. A number of case histories of patients who at first denied anxiety but who exhibited an anxiety reaction were included. The anxiety reaction has been found useful in discovering delu-

sions of persecution when concealed by psychotic patients. If a psychotic patient makes defense movements, however slight, when his knee jerks are elicited, the examiner should be very persistent in searching for delusions of persecution. Another reaction studied is tremor of the eyelids when the patient is in the Romberg posture. This in my experience has occurred in the presence of phobias. In almost all cases it has been a phobia for high places, acrophobia. Probably this is because that phobia occurred many times as often as any other in this series of cases.

In 148 functional cases with an anxiety reaction, 142 patients admitted anxiety and 6 denied it. In 90 functional cases in which there was no anxiety reaction, anxiety was present in only 10. Of 12 malingerers, only 2 had an anxiety reaction. Of 18 psychotic patients, only 4 had an anxiety reaction and these were the only ones who had delusions of persecution.

I believe that the tendon reflexes are the remains, after evolution, of larger and more generalized movements, primarily defensive in nature and in purpose. While testing the reflexes of a patient there is much that may be discovered, besides the presence or the absence of lesions, if one will take a larger view and, instead of fixing one's attention on the quadriceps muscle or achilles tendon, will watch the whole body of the patient. There are psychic or cerebral reflexes as well as spinal cord reflexes that one should train oneself to see.

DISCUSSION

DR. DONALD GREGG: How do you distinguish between anxiety reaction and muscular hypertonus?

DR. H. POWERS: I did not refer to an increased knee jerk as a manifestation of an anxiety reaction. Hypertonus may be made out by palpation.

EXPERIMENTAL COMBINED SYSTEM DISEASE. DR. EDWIN GILDEA, DR. E. E. KATTWINKEL and DR. W. B. CASTLE.

The general nature of the response of pernicious anemia to the feeding of liver indicates a deficiency disease. Recently published observations by Dr. Castle suggested that the deficiency is dependent for its production on the achylia gastrica characteristic of the disease. The almost invariable association of achylia with the symptoms of spastic paralysis and disturbances of sensation in the legs in cases of pernicious anemia, pellagra and sprue prompted the study of the neurologic symptoms as also possibly related to a deficiency mechanism inherent in the achylia gastrica. A review of the literature revealed the fact that diets deficient in vitamin B, when fed to animals, had been reported to produce changes in the gastro-intestinal tract and reduction in the gastric secretions, together with neurologic signs usually described as polyneuritis. Of particular interest were the observations of Cowgill of a condition in dogs fed diets deficient in vitamin B in which gastro-intestinal symptoms and a spastic paralysis, first affecting the hind legs, were prominent features.

Consequently, eight dogs (series A) were placed on a diet deficient in both factors of vitamin B and of the type that has been demonstrated to be otherwise adequate by McCollum and others. A second series (series B) were given an identical diet, except for the addition of autoclaved yeast, to supply the pellagra-preventing factor of vitamin B. A third series (series C) were fed a diet which Goldberger has demonstrated to be deficient in the pellagra-preventing factor of vitamin B. Studies of the symptomatology, gastric analyses, blood counts and postmortem examinations were made. In view of the fact that Hofmeister has shown that animals fed on diets completely deficient in vitamin B sicken and die rapidly, without showing marked symptoms of paralysis, an effort was made to produce a chronic partial deficiency by feeding the animals small doses of vitamin B extract whenever they seemed to be on the verge of death. On this regimen some animals lived for from 100 to 200 days and showed repeatedly prompt relief from symptoms with vitamin B. In dogs in series A and B severe symptoms

developed after from the sixtieth to the eightieth day. These consisted of loss of appetite and weight, progressive weakness and stiffness of the legs, spastic paralysis, convulsions, coma and death. Peripheral reflexes were ordinarily present even with marked paralysis. Dogs of series C, lost weight and appetite, and they became mangy. Scaling skin lesions developed, and finally the dog died in convulsions, without showing severe paralysis or spasticity. No significant changes in the response of gastric secretions to histamine were observed in any of the animals and in some a slight secondary type of anemia developed.

Parts of the brains and cords were fixed in formaldehyde, and in Müller's fluid, and stained with hematoxylin and eosin, cresyl violet, scharlach R, and by Weigert's and Spielmeyer's technics. The Marchi and scharlach R stains were used on the peripheral nerves. In the dogs of series A and B, the most marked lesions were found in the cord, and the next in the cerebral cortex; the peripheral nerves were least affected. The lesions in the central nervous system consisted of diffuse and irregular loss of myelin, with patches of almost complete demyelinization. The edges of such patches shaded gradually into almost normal white matter. In these border areas most of the nerve fibers had irregular swellings that gave them a beaded appearance. Such changes were most obvious in the sections stained by the Spielmeyer method. No evidence of an inflammatory process or of glial proliferation could be found in any of the dogs. Little or no fat could be found in the perivascular or meningeal spaces of the cord by the scharlach R stain, but a considerable amount was found in perivascular spaces of the cortex and in some of the nerve cells. Cresyl violet stains brought out swelling and chromatolysis of the nerve cells of the cord and cortex. Scharlach R stains of peripheral nerves showed patchy degeneration of myelin in nine of the animals, much less severe than in the cord and cortex. The dogs of series C showed only the early stages of the lesions found in series A and B.

It was concluded from these experiments that vitamin B deficiency, if prolonged for a sufficient length of time, produced a demyelinization chiefly of the white matter of the cord and cortex and to a less extent of the peripheral nerves; that previous workers have not sufficiently stressed the importance of the lesions of the cord, in contrast to those in the peripheral nerves. It was also pointed out that the lesions of the cord resembled closely those found in the so-called combined system disease of pernicious anemia.

Since no significant changes in the gastric analysis were manifest, no essential relationship between achylia gastrica and these lesions was demonstrated. The resemblance of the lesions produced in this experiment by the deficiency of antineuritic vitamin B to those occurring in man in the presence of achylia gastrica suggests that the achylia of such conditions may in some way condition a virtual deficiency of that vitamin in spite of its presence in the ingested food.

Regular Meeting, Jan. 16, 1930

DONALD MACPHERSON, *President, in the Chair*

ARE THERE END ARTERIES IN THE BRAIN? DR. STANLEY COBB.

This paper will be published in full in the ARCHIVES.

ACUTE MULTIPLE SCLEROSIS IN DOGS. DR. TRACY PUTNAM.

A large number of cases of a distinct type of disseminated encephalomyelitis have been reported at various times and under various names, such as neuromyélite optique aigue, multiple degenerative softening and acute multiple sclerosis. This last name is a misnomer, as there is no sclerosis, although the disease may have some connection with multiple sclerosis. It is not always recognized that

a similar condition has been twice encountered by accident in dogs, once by Claude (*Arch. de Physiol. norm. et path.* **29**:843, 1897) as a result of the injection of tetanus toxin, and once by Ceni and Besta (Riv. sper. di freniat. **31**:125, 1905) as a result of infection with *Aspergillus fumigatus*.

The present investigation aims at elaborating their chance discovery. Of forty-six dogs inoculated with minimal doses of tetanus toxin under various conditions, two showed paralysis and ataxia. Both showed an increase of cells and proteins in the spinal fluid. One of these was still alive, and was presented before the Society. The other died in April, 1929, and preparations showed the presence of a large number of discrete patches, somewhat more frequent in the white matter, of myelin degeneration and perivascular infiltration. There was slight proliferation of neuroglia, but the exudate was predominantly lymphocytic. Changes in nerve cells and axons were inconspicuous. There were no tract degenerations. There was a mild thickening and cellular infiltration of the meninges. The optic chiasm and nerves contained a plaque of demyelination and cellular exudation that involved only a portion of the cross-section.

Why the disease should occur in these animals and not in others in the series is not clear. Gross dietary deficiencies and ordinary kennel epidemics can apparently be excluded. The tentative conclusion may be drawn that the tetanus toxin acts as an exciting cause, but that some other unknown factor is also involved.

DISCUSSION

DR. G. C. CANER: Do you believe that removing the spinal fluid had anything to do with the development of the symptoms?

DR. T. PUTNAM: I wish I knew. I am proceeding to do that to three other dogs, so far without results. I think that one must try it and see. I am also treating others with carbon disulphide and tetanus toxin.

THE RELATIONSHIP BETWEEN THE LOCATION OF BRAIN TUMORS AND THEIR MANIFESTATIONS. DR. FREDERIC A. GIBBS.

This report is based on a detailed study of the clinical histories and autopsy reports in 203 cases of tumor of the brain. Each case was analyzed on a seventy-six column chart. The columns were headed: location of tumor, type of tumor, choked disk, vomiting, generalized convulsions and so on. Forty-two symptoms were studied. The grouping and laterality of tumors producing a given symptom were analyzed. A table was arranged to show the correlation of the symptom with the position of the tumor. Another table was arranged to show the correlation of symptom with symptom.

In this series there appears to be some relationship between the position of the tumor and the side of greater choking. The relationship is expressed by the following tendencies: 1. When unequal choked disk is produced by a unilateral tumor, if the tumor involves the temporal lobe, the greater choking tends to be on the same side (in all of 4 cases). 2. When unequal choked disk is produced by a unilateral tumor, if the tumor does not involve the temporal lobe the greater choking tends to be on the opposite side (in 9 of 11 cases). 3. When unequal choked disk was produced by a bilateral tumor involving one side more than the other, the greater choking tended to be on the opposite side (in 5 of 6 cases). 4. When unequal choked disk was produced by a bilateral tumor behind the infundibulum, the greater choking tended to be on the right (in 17 of 19 cases).

The theory that the degree of choking is conditioned by the pressure in the vena centralis retinae is proposed to explain these tendencies.

1. Tumors producing greater choking on the same side were ideally situated for pressing on the venous channels directly draining the fundus. Such interference would result in a higher pressure in the central vein of the retina on the same side.

2. Tumors producing greater choking on the opposite side were ideally situated for compressing one of the lateral sinuses or one of the large veins draining to the base. Such interference would reduce the venous pressure in the cavernous sinus and in the central vein of the retina on the same side, and, because flow would be shunted to the opposite side, there would be an increased pressure in the cavernous sinus and central vein on the opposite side.

3. Bilateral tumors involving one side more than the other are so situated that they block side to side anastomoses, thus cutting down the amount of shunting that can take place and making it likely that the greatest effect will be produced by pressure on the channels draining the fundus, a type of interference that would be greater on the side of greater involvement.

4. Tumors of midline structures behind the infundibulum are well situated for interfering with flow from the vein of Galen or the straight sinus. The vein of Galen empties into the straight sinus and the straight sinus, in 75 per cent of all cases, empties into the left lateral sinus, so that blockage of either the vein of Galen or the straight sinus would result in a decreased pressure in the left lateral sinus, in the left cavernous sinus and in the left central vein, whereas there would be a less marked reduction in pressure in these channels on the right, and in the case of the right central vein the pressure might even be raised.

A model of the veins of the brain was constructed according to accepted descriptions of the intracranial venous system. The pressure shifts, incident to the compression of a given vessel, were such as have been described in offering a theoretical explanation for the manner in which side of greater choking varies with tumor position.

On studying the grouping of tumors producing a given symptom it was found that the following symptoms were produced by supratentorial tumors tending to group at the base: generalized convulsions, impairment of memory, aphasia, olfactory hallucinations, gustatory hallucinations and no vomiting; whereas the following symptoms were produced by tumors tending to group above the base: focal convulsions, visual hallucinations, irritability, jocularity, incontinence of urine, difficulty in micturating, projectile vomiting and high grade choked disk. The symptoms listed as being produced by supratentorial tumors tending to group at the base were produced more readily by unilateral supratentorial tumors on the left, while those listed as being produced by supratentorial tumors tending to group above the base were produced more readily by unilateral supratentorial tumors on the right. Tumors producing a given symptom did not tend to lie in the functional area usually associated with that symptom; they tended to lie across one of the large venous channels draining that area, which suggests that interference with venous drainage is a factor in the production of symptoms. Such an hypothesis would explain the grouping of tumors producing a given symptom: The largest vein draining the cortex empties into the cavernous sinus (at the base), and the largest vein draining the noncortex empties into the straight sinus (above the base). On such a theory the laterality of tumors producing a given symptom becomes less difficult to explain. The only assumption necessary is that there is an asymmetry of the intracranial venous system which permits supratentorial tumors on the right to interfere more with venous drainage from certain areas than similar tumors on the left and vice versa. The asymmetry of the torcula and the relationship of such an asymmetry to supratentorial drainage tends to support such an assumption.

The production of signs and symptoms by interference with venous drainage offers a possible and plausible explanation for some of the symptomatology of tumor of the brain that is otherwise difficult to explain.

DISCUSSION

DR. DONALD GREGG: If the patients were all right handed, would that not possibly bring in a variation in your figures on aphasia as regards tumors on the right side? What is meant by jocularity? Do you mean an unusual tendency toward laughter, or a tendency toward increased humor and smutty stories, which

one sometimes observes in cases of tumor of the brain? My reason for asking is that a Frenchman has recently reported that laughter may possibly be explained by a varying basal motor tone; and the symptoms on the right side—irritability, urinary incontinence, etc.—would possibly go in more with basal motor variations and would fit in with jocularity, if by that you mean laughter.

DR. GILBERT HORRAX: In regard to the question of choked disk, I supposed that the theory was pretty well established that choking was due to mechanical pressure on the side of the tumor or the opposite side, and was pretty well explained by Parker's work. While your view is interesting I do not understand that it is absolutely necessary to offset Parker's observations. In the explanation of these symptoms of venous pressure it is interesting to approach it from this point of view, especially in regard to explaining those cases in which one does not find the exact localization expected. One may then well resort to some method such as this to explain the symptoms.

DR. HENRY VIETS: Have you applied this theory at all to venous sinus thrombosis, which would be almost experimental in respect to the development of choked disk, provided the theory is tenable?

DR. F. A. GIBBS: It was unfortunate that in a good many of my cases I had to omit information as to whether patients were right or left handed; this point was so seldom found in the histories that I could not consider it, but it is interesting that tumors tending to produce aphasia were on the left side and were in line with other cortical symptoms. I know that there is a center for speech control on the left side for right-handed people which has no counterpart on the right. I am sure a great deal of evidence has been provided by tumors which have interfered more readily with these cortical areas on the left, and that lesions on the right are incapable of producing aphasia. This is all theory, and I do not wish to defend it too warmly because it has yet to be proved. The term jocularity covers a symptom that was not sufficiently defined in the histories of my patients to allow of any careful analysis, but merely as a sort of total reaction; by that, I think that probably most of the physicians who recorded the histories meant something akin to uncontrollable laughter, which I imagine to be a psychic form, but both symptoms must have a rather deep vegetative origin and as such it might be possible to classify them together as jocularity and call them noncortical symptoms.

The material used was clinical histories and autopsy reports. In some cases I was particularly interested to find whether there was dilatation of the ventricles. It is unfortunate that it was impossible actually to examine some of the brains. However, ever since he has been at Johns Hopkins, Dr. Macallum, in his autopsy reports, has made notes on the position of the tumor in the brain (except for a brief period when they were examined by some one else). He has started his notes in each case by saying merely to what particular region the tumor extended in front, a proceeding which might not be satisfactory to a neurologist. He sections brains as though they were the leaves of a book; then he tells how far the tumor extends to either side and changes the width as he goes back, as necessary, and then he notes where the tumor stopped, so that in each case I was able to find the position of the tumor fairly accurately. I know that this is not the method that would receive much recognition from expert neurologic investigators, but it is one which seemed fairly satisfactory since, with as many cases as 200, I could not have done more by studying them in detail. I did make an attempt to apply the method to cases of venous sinus thrombosis, but unfortunately in most of the cases I could find (and there were not many) the nose and throat physicians who had them had not made careful observations on the amount of choking. I am glad that this has been brought up, for it is exactly what I am trying to do on animals in the laboratory. I probably did not bring out what I wished to. I do not say that choked disk is produced entirely by interference with venous drainage; that is, the choking may be produced by the cerebrospinal fluid pressure, but it will be higher or lower in one eye or the other according to whether the venous pressure is higher or lower in one eye or the other.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 20, 1930

LOYAL DAVIS, M.D., *President, in the Chair*

PATHOLOGIC REPORT: TORULA MENINGO-ENCEPHALITIS. DR. ARTHUR WEIL.

The case of *Torula* infection of the meninges and the brain which is presented, corresponds in its main features with the characteristics of similar lesions as described by J. L. Stoddard and E. C. Cutler (Monograph 6, Rockefeller Institute for Medical Research, New York, 1916). But in two points it did not fulfil the schematic requirements which they deduced from a comparison of their own two cases with ten others published previously.

1. The course of the disease in this case (a white woman, aged 25, pregnant for three months) was an acute and not a chronic one. Beginning on October 27 with tiredness and weakness, following a sore throat, there were complaints of headache and vomiting on October 30. A remission occurred for a few days; then there was bleeding from the nose with vertigo on November 5. The patient was listless and stuporous on November 7, and died on November 15, after twenty days of illness. This case therefore showed features similar to that in the case reported by von Hansemann, of nineteen days' duration.

2. In sections from alcohol-fixed material stained with different aniline dyes and impregnation with silver, the granulomas in the cortex did not show the frequently described "soap-bubble" appearance, but they were rather homogeneous. No liquefaction of the adjacent brain tissue could be noticed; there was only a compression of axons and glia fibers by growing and extending *Torula* cells. In formaldehyde-fixed material, however, the soap-bubble like appearance was readily seen, also the star-shaped gelatinous mass surrounding the larger *Torula* cells. It is suggested, therefore, that the suffix "histolytica," be omitted, because it seems that the coagulating action of the formaldehyde on the gelatinous matrix surrounding the yeast cells produces the histologic pictures which have been described as representing histolysis. Besides, the fermentative action of *Torula* is only minimal as compared with that of cultured yeasts. It is reduced almost to nothing in the presence of oxygen, as Meyerhof's experiments convincingly demonstrated.

DISCUSSION

DR. G. B. HASSIN: The pictures demonstrated by Dr. Weil differed greatly from those I have seen and those observed by others. In the case of Kaplan and Rappaport, pathologic specimens of which I have seen, there were, grossly, areas of liquefaction without any reaction on the part of the glia or the blood vessels. The difference may be explained by the time element. Dr. Weil's case was of only eighteen days' duration, while the one I saw was a year old or more. Perhaps by that time the tissues had had a chance to become destroyed and liquefied, a condition which was not so marked in Dr. Weil's case. I think that the method of fixation of the material is hardly responsible, for in no other pathologic condition is there present so marked a difference due to fixation.

DR. WALTER FREEMAN: *Torula* meningitis has been a hobby of mine and I now have material from sixteen cases. The histologic features of some are very different from those of others. Dr. Weil has shown an unusual type in that the lesions are very compact. I attribute this to the duration of the illness, as Dr. Hassin suggested. In some of the acute cases that I have seen, there is a spreading out of the organisms; they break through the mesodermal barrier and invade the nervous tissue itself. It seems to me that the dissolution of tissue and the great dilatation one finds in the cavities are due entirely to the growth of the yeast, since in the walls of these cavities one can find nerve fibers. Fat is almost nonexistent; the cells are changed, but retain their granular element.

Dr. Weidman, my collaborator, is a good mycologist, but so far as the taxonomic position of the organism is concerned, he is still uncertain where the organism belongs. We believe that *Torula* is the best place to put it on account of the lack of the mycelial and spore formation. Torulosis is to be differentiated from many cases of blastomycosis.

DR. PETER BASSOE: Will *Torula* ferment any kind of sugar in all of the usual cases?

DR. ARTHUR WEIL: I regret that I did not present more lantern slides in order to demonstrate the difference in the histologic appearance of alcohol and formaldehyde-fixed material. They might have explained why Dr. Hassin thought that the histologic pictures seen by him in the case of Rappaport and Kaplan, with their soap-bubble like appearance, differed from those presented, which were photographed from alcohol-fixed preparations. Freeman and Weidman (Cystic Blastomycosis of the Cerebral Gray Matter, ARCH. NEUROL. & PSYCHIAT. **9**:589 [May] 1923) remarked that in the fresh brain, no evidence of pathologic changes was seen in the cortex with the naked eye, but that after formaldehyde fixation, the small cyst formations were visible. I regret that I cannot answer Dr. Bassoe's question. It seems that until now only dextrose has been used for fermentation experiments in *Torula* cultures.

A REPORT OF THE FIRST YEAR'S WORK IN MENTAL HYGIENE IN THE HEALTH SERVICE OF THE UNIVERSITY OF CHICAGO. ROSE SENIOR (by invitation) and JOHN FAVILL.

This report will be published in full later.

MENTAL TREATMENT OF TUBERCULOSIS. DR. B. A. THOMPSON (by invitation).

In addition to combinations with diseases of the nervous system, such as multiple sclerosis, tabes and dementia paralytica, tuberculosis may be combined with manic-depressive or schizophrenic psychoses. Such conditions require appropriate treatment. There may, however, also be combinations with neuroses, which I regard as differing from the psychoses only in that in the former there is a partial submergence from reality, while in the psychoses it is complete. I do not believe that there is any distinct personality group in patients afflicted with tuberculosis. The so-called organic disturbances in the tuberculous patient are capable of bringing to light psychic material of a kind that does not reflect the actual dispositions of the personality of the patient. Yet tuberculosis is three times as prevalent in the schizoid groups as in all the other three groups together. Schizoid psychoses are, from a psychologic point of view, noncompensatory or decompensating; that is, the patient with dementia praecox on the whole, shows little active tendency to get well or to develop a compensatory type of reaction. In harmony with this type of reaction at the psychologic level, one finds at the somatic level a similar type of reaction to the infection of tuberculosis. Such persons not only are easily infected, relatively speaking, but easily die of tuberculosis. In a review of these cases one finds a general uniformity of personality: hindrance to self-expression, jealousy, day-dreaming, compulsions, visual disturbances, release of primitive trends, dissociative trends and deeply rooted regressive features.

The spes phthisica, commonly observed in adults but not in children, is a compensatory reaction for the depression and suicidal trends which are present in the unconscious life of all patients. This factor is present probably in all forms of chronic illness. The cause of the pathologic hope is to be found in an inferiority complex; there is a childish dilapidation; patients respond well to encouragement and childish offers which stimulate good behavior. Such patients plan for the future, feel fine and talk in a jocund manner; the fact that they have only a few months to live causes a split of personality and the hopefulness is an unconscious insight or compensation for the physical deficiency. Fear in the tuberculous

person is also in need of analysis. One will find the cause of many depressions in this disease in deep-rooted anxieties which have become "out of bounds," as it were. Definite fear complexes of this type are frequently shown in dreams and are often disguised in symbols. Simple discussions may be all that is necessary to relieve the more superficial fears, but for those that are deeper, closer analysis is needed. There is a similar situation in other forms of emotion. One does not rail at the stubborn, or condemn a patient with tuberculosis who is irritable, fault-finding, argumentative, deceitful or rebellious. Instead, one endeavors to find the why of these reactions and study his or her complexes, conflicts and difficulties.

The toxic element in this disease is a fertile ground on which may occur many affective disorders, neuroses and even psychoses. It should be understood clearly, however, that in this statement I do not express the belief that the toxic condition causes these states per se, but rather that it may so undermine the patient's psychic equipment as to permit the development of mental symptoms. True toxic psychoses may occur, however, as in other somatic diseases.

In the treatment of the patient, it is important that the physician gain his confidence; for this end it is essential that the physician have confidence in himself. Give the patient proper but not false encouragement; allow him to tell his story fully and endeavor to enter into all the facts in his situation, in addition to his disease. Sublimation of the energies can be accomplished by proper reading, occupational therapy, amusements, graduated exercises, etc. Psychoanalysis and suggestion are important elements in treatment. Institutions are valuable to stimulate a proper attitude of the patient toward cure and to afford the physician an opportunity to play the rôle of educator. After such schooling the patient can go home and carry on properly.

THE MALARIAL TREATMENT OF DEMENTIA PARALYTICA: CEREBRAL AND EXTRACEREBRAL PATHOLOGY AND ITS BEARING ON THE MODUS OPERANDI. WALTER FREEMAN, Washington, D. C. (by invitation).

A study of the extracerebral pathology in patients with dementia paralytica following therapeutic malaria was undertaken in the hope that it might answer the pregnant question: Does malaria kill the spirochete, or does it merely suppress its activities in the central nervous system? The premise was taken that if the indications of syphilis were no more marked in the rest of the body than they were in the brain, the evidence would be in favor of sterilization, whereas if syphilitic lesions were well marked in the body and absent from the brain, the evidence would be in favor of some alteration in the tissues of the host inimical to the continued development of the spirochete in the central nervous system. The chief objections to this plan of study were that the duration since malaria was rather short (maximum, five years), and that the lesions probably begun by the spirochete in the aorta, liver, etc., might be carried on by other agents. In order partially to offset the difficulty, two cases of spontaneously arrested dementia paralytica, of twelve and fifteen years' duration, respectively, were included.

Seventy-one patients who had been inoculated with malaria were studied. Twenty-six had had no paroxysms and therefore served as controls. The average duration of life after inoculation was four and one-half months. Twenty-three died within two months of the cessation of malaria. The occurrence of cirrhosis of the liver in eight cases indicated the risk from malaria in such patients. Lesions of the aorta were fairly common but did not seem responsible for death. Nine patients lived more than two months after the cessation of malaria but showed persistent active inflammation in the brain. Thirteen patients survived the malaria more than two months and showed no active inflammation in the brain. Study of this last group showed that the evidences of syphilitic inflammation in other viscera were more marked than in the group that showed persistent dementia paralytica. In certain cases, although the brain showed only the sclerosis and vascular changes of arrested dementia paralytica, there were active productive

inflammatory processes in the cardiac muscle, in the aorta, in the liver, and occasionally in the pancreas, testis and lung. One patient died of a ruptured aneurysm eighteen months after malaria, one of ruptured bladder, one of cerebral hemorrhage after a rather slight injury, and two died in statu quo. On the whole, however, death usually resulted from some cause not associated with the nervous system. In the unsuccessful cases, aside from two instances of tuberculosis, death resulted directly from the terminal complications of dementia paralytica. The two cases of spontaneously arrested dementia paralytica showed marked cirrhosis of the liver, probably syphilitic.

The conclusion was reached, therefore, that there were definite indications of persistent syphilitic processes in the rest of the body even though the lesions in the nervous system were arrested. The small number of cases, the relatively short duration after malaria, and the greater age of the subjects in the successful group were possible explanations of the discrepancies, but the evidence was in favor of some alteration in the neural parenchyma that brought about an arrest in the syphilitic process while allowing it to persist in the other organs.

Among the factors that might eliminate the spirochete from the central nervous system, three were considered of importance: The high fever during the paroxysms might prove lethal to the organisms; the activation of the reticulo-endothelial system might furnish the nervous system with better defenses against the organism, and the forced drainage of the nervous system during fever might bring about evacuation of the organisms as well as the perivascular exudates from the neural parenchyma into the subarachnoid spaces. The spirochete might be considered as being more defenseless in the central nervous system on account of the tenuity of the fibrous connective tissue, which, in other organs of the body, might form nests for it, impregnable to the wandering cells or protective fluids of the body.

The hydration mechanism and the tenuity of fibrous connective tissue seems to explain most satisfactorily the clearing up of the inflammatory process in the brain with its persistence in the other viscera.

Therapeutic conclusions are advanced tentatively. Patients with aortic and myocardial disease often come through the rigors of induced malaria surprisingly satisfactorily, but those with hepatic lesions are bad risks. Patients subject to convulsions and juvenile patients with dementia paralytica, have a poor outlook. The material is too small to determine whether treatment with arsenic before malaria is either beneficial or harmful. The outstanding failure of the series was in the patient who had received the most treatment, and some of the best results were obtained in patients who had had no previous antisyphilitic therapy. In view of the occurrence of syphilitic lesions elsewhere in the body, it would probably be advisable to follow the malaria with treatment by the arsenicals, although the serologic reactions may slowly become reduced to normal even without such postmalarial treatment. Other pyretogenic agents besides malaria are fairly effective in the treatment of dementia paralytica, but there are indications that malaria combines most effectively the three factors mentioned (high fever, stimulation of the reticular system and forced drainings of the brain) in ridding the central nervous system of the invading treponema.

DISCUSSION

DR. G. B. HASSIN: Time would not permit a detailed discussion of this extensive paper. Dr. Freeman tried to prove that a brain damaged by dementia paralytica can be reconstructed by the plasmodia of malaria; that actual anatomic changes can take place. These changes show, in his opinion, mainly as mildness or lack of adventitial cell infiltrations. However, this may occur in patients who never had malarial or any other treatment, and a mild adventitial cell infiltration does not denote an improvement in the clinical picture and vice versa. Dr. Freeman said nothing of the parenchymatous changes, but laid great stress on the perivascular accumulations of lymphocytes and plasma cells. In their extensive studies, Globus and Michels showed conclusively that the foregoing elements come from

the inside of the blood vessels to invade the adventitial spaces; this is in contrast to what I could gather from the foregoing demonstration, that the blood cells plunge back into the vascular lumen. Of the numerous explanations of the beneficial effect of the malaria treatment of dementia paralytica, the most interesting is the one offered by Sträussler. He adopted Jakob's interpretation that dementia paralytica is a malignant nonspecific type of syphilis which is rendered by treatment benign and specific. Such a view, however, was strongly opposed by Spielmeyer. Can Dr. Freeman give any confirmation of Jakob's views? My impression is that the effect of malarial treatment is due to the metabolic changes that take place in the cerebral parenchyma, which cannot be shown under the microscope.

DR. CHARLES F. READ: Dr. Freeman spoke of not coming into contact with other work on other organs than the brain, in patients treated with malaria. Recently I came across an article by Lehoczky (*Arch. f. Psychiat.*) in which he detailed his observations on other organs of the body, and stated that he failed to find any particular reaction on the part of the reticulo-endothelial system. He was of the opinion that there is no healing reaction in the direction of ordinary tertiary syphilis. It is a very interesting and well written article on this particular point.

DR. A. B. YUDELSON: I have had a series of twenty-one patients with dementia paralytica, treated with malaria. During the occurrence of the paroxysms, the spinal fluid was withdrawn and studied. In none of the cases was the serology changed materially. Two of the patients were inoculated with malaria from a malarial, not a syphilitic, patient, and they lived the longest. I tried clinically to rule out syphilis in other parts of the body as far as I could.

Has Dr. Freeman observed any changes in the spinal fluid during the febrile periods? Is there more merit in malaria from nonsyphilitic than from syphilitic patients?

DR. WALTER FREEMAN: I realize that the topic raised a number of controversial questions, and appreciate the interest shown in the discussion.

In regard to Dr. Hassin's remarks regarding degenerative changes, I have to confess that either my eye or my mind is somewhat blind to the cytoplasmic changes that occur in the ganglion cells. The cytoplasm is so subject to degenerative changes from any cause that I attach more importance to the changes that take place in the architecture than I do to the intimate cellular change. I often find patients who show little perivascular change, and I think that in those patients the symptoms were due to the architectural changes. I think that this means more from the functional point of view than the changes found in the ganglion cells. I do not wish to correct Dr. Hassin, but it is Bruezsch's opinion that the mononuclears pass into the blood vessels to become phagocytes. I can observe these cells passing through the walls of the vessels, but I do not know whether they are going or coming.

Jakob, I think, has modified his stand on dementia paralytica and malignant syphilis of the brain, but gummas are unusual. I have found them in only one or two cases.

The metabolic changes in the ganglion cells that cannot be seen with the microscope are of interest. I recently reported what I considered to be a significant deficiency of iron in the cells in schizophrenia. The improvement that one sees in patients with dementia paralytica, I think, is due to the cleaning up of the architecture of the cortex, the reestablishment of the ganglion cells and possibly their realinement in the proper planes. In the cortex I have shown, I think, that the lamination or polarity is better than that which you will find in the mild or average case of dementia paralytica.

As to Dr. Read's question, I think that the reports of Lehoczky to which he referred deal with acute cases. These observations are sound, however, and if he had had material that lasted for a long time after malaria, he might have found the same changes. We investigated the neuroglia in certain patients who were

suitable, and in those cases in which the cleaning up of the inflammatory reaction was satisfactory and no inflammatory cells were found, the neuroglia seemed to have reverted largely to the protoplasmic type. The oligodendroglia is so difficult to impregnate successfully that it was not studied in detail. I think that in the older cases, in which the process has gone on to a marked atrophy of the parts, there is a marked increase in the fibrous neuroglia at the margins.

I am glad that Dr. Yudelson has had an opportunity to study the serology during the paroxysms. This should be done during water intoxication. I would suggest that the best time for such a study would be during the height of the fever, as this would indicate whether the cells were being washed out from the perivascular spaces into the subarachnoid spaces.

As to the results from inoculating patients with blood from other patients with dementia paralytica or from nonsyphilitic patients, I do not see why, a priori, there should be any difference. It has been the policy of Dr. White to allow only blood from nonsyphilitic patients to be inoculated. Our clinical results compare favorably with those reported elsewhere.

A Fever Treatment of Dementia Paralytica by Injection of Sulphur in Olive Oil. Dr. Charles F. Read.

Following up the work of Knud Schroeder, as reported in various Danish and German publications during the past few years, and more recently in the *Lancet* (Sulfosin Treatment of General Paralysis and Other Disorders, *Lancet* **2**:1081 [Nov. 23] 1929) I began the treatment of patients with dementia paralytica by suspensions of sulphur in olive oil, in the fall, 1929. A small group of patients under treatment since that time has shown some encouraging results, which seem in every way comparable to those secured in a much larger group treated with malaria and reported some years ago.

Treatment has been given, after Schroeder's technic, by means of intramuscular injections—best into the abductors of the thighs, occasionally into the glutei—beginning with from 1 to 2 cc. of a 1 per cent suspension of sublimated sulphur in olive oil in 5 and 10 cc. ampules. When injection is made at between 7 and 8 p. m., the temperature begins to rise early in the morning of the next day, reaches its height (from 103 to 104.5 F.) at about noon, holds this for from one to three hours and then declines to from 101 to 102 F., where it may remain for several hours before sinking to normal.

The dose must gradually be increased according to the patient's reaction, as in typhoid vaccine therapy. Now and then, fever persists for from twenty-four to forty-eight hours when the larger doses of from 8 to 10 cc. are reached, and a 2 per cent suspension may be substituted, the dose of which must be a little larger than the exact equivalent of the 1 per cent suspension. Occasional rest periods of a week or ten days are advisable.

A marked local reaction develops as the fever rises, and persists for about thirty-six hours. In view of this and the occasional persistence of the fever for a like period, injections cannot well be made oftener than every three days. Abscesses do not occur, and chills and headache are rare. High white blood counts are the rule, from 20,000 to 35,000. Reductions in blood pressure (during the height of the fever), in weight and in red cells and hemoglobin occur, but are insignificant. Some Wassermann tests of the blood have been greatly reduced, but the spinal fluid condition has been unaltered thus far.

The modus operandi of the febrile reaction is obscure; a systemic reaction develops with the local irritation and seems to depend on it. Schroeder suggested the specific action of sulphur-albumin combinations formed at the site of the injection. Insufficient time has elapsed to warrant more than tentative conclusions as to remissions and improvement; also, the group is small as yet; only eight patients thus far have been dismissed to be placed on treatment with

tryparsamide. Results thus far, however, have been eminently encouraging, and the method is so safe and so simple as to warrant further trial with the thought that it may eventually find a place in the treatment by fever in dementia paralytica.

DISCUSSION

DR. G. W. HALL: I am interested in this communication because the charts disclosed the duration of the fever, which is longer than in any other form of treatment with which I am familiar. The essayist seems to regulate this fairly well by the dosage.

I should like to know if when the solution is injected into the gluteal region there is any local disturbance and if the treatment is painful.

DR. WALTER FREEMAN: I should think that these injections of sulphur would be particularly applicable in patients who are likely to suffer from myocardial trouble, and also for the negro, who seems to take malaria unsatisfactorily. I am interested in this type of treatment, not having heard much of it before, and shall be glad to learn of further work.

DR. CHARLES F. READ: These patients present a local reaction which is very considerable at times in the gluteal region, less so in the abductors of the thigh. There has been no abscess formation. It seems necessary to allow a rest period if one is going to give more than from ten to twelve treatments. Some of my patients have not been sufficiently treated, but because one had to admit other patients, they were moved along as soon as they presented fairly good improvement.

This method seems to be indicated for patients who are not suitable for malarial treatment and in some cases in which it is not convenient to give intravenous therapy. It is not presented as a new departure that will revolutionize fever therapy, but as an interesting investigation. It may find a place in the febrile therapy of dementia paralytica on its own merits.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 28, 1930

WILLIAMS B. CADWALADER, M.D., *President in the Chair*

PRELIMINARY NOTES ON BACTERIOLOGIC STUDIES AND TREATMENT OF CHRONIC ENCEPHALITIS. DR. WINIFRED B. STEWART and DR. MARY JARDEN EVANS.

This paper will be published in full elsewhere.

A PRESERVATIVE FLUID WHICH RETAINS THE COLOR AND NORMAL RELATIONS IN THE NERVOUS SYSTEM WITH SOLIDITY FOR SECTIONING AND DEMONSTRATIONS WITH SYMPTOMS. DR. A. HEWSON.

On Dec. 29, 1903, I presented to the Association of American Anatomists, at Philadelphia, "A Method of Preparing Brains to be Used in Class Demonstration" obtained by the following formula: sodium arsenate, 2 Kg.; potassium nitrate, 1 Kg.; glycerin, 2,000 cc.; water, 7,700 cc.; formaldehyde (40 per cent solution), 150 cc., and phenol (deliquescent crystals), 150 cc.

Boil the salts in water to solution; dissolve the carbolic acid in glycerin and then add the formaldehyde; finally, mix the salt solution and the glycerin, phenol and formaldehyde. The completed solution was injected into the cadaver, the brain removed shortly (two or three days) thereafter and each specimen placed in separate vessels.

The nervous system preserved its color and did not bleach much; as the specific gravity was over 1.265, the brain floated and the relations were preserved.

On Nov. 11, 1915, I presented to the Pathological Society of Philadelphia, from work done in the laboratories of the Philadelphia Polyclinic, the following formula: Solution 1: borax, 1,800 cc.; boracic acid, 1,200 cc.; potassium nitrate, 7,000 cc.; boiling water, 121,000 cc.; arsenious acid, 500 cc.; rock salt, 15,000 cc.; phenol, 500 cc., and glycerin, 16,000 cc. Solution 2: thymol, 30 cc.; acid salicylate, 180 cc.; alcohol (95 per cent), 25,200 cc., and formaldehyde, 1,800 cc.

In making solution 1, the borax, boracic acid and potassium nitrate are dissolved in boiling water; then to a portion of the water, the arsenious acid, rock salt and phenol, dissolved in the glycerin, are added. In making solution 2, the acid salicylate and thymol are dissolved in the alcohol, and the formaldehyde is added. The two solutions are mixed, and the preparation is ready for use. This solution had a higher specific gravity than the 1903 solution, the disadvantage being that it allowed the brain to be too soft; with the addition of more formaldehyde this disadvantage was overcome.

The phenol discolored the solution as the specimens were kept, but had no effect on the color of the specimen. Visceral specimens, taken post mortem, could be immersed and put in the sun, which had no effect on the color of the specimen. The drawback, as stated, was in the change produced by the phenol, darkening the solution.

Since 1918, I have found that any solution containing phenol with the foregoing ingredients takes on this brown color, possibly due to oxidation, but if mixed fresh, the phenol being withheld until the last, the solution makes a better preservative; later I found that if only parts of each were used, I could obtain better results.

I therefore evolved the following formula for a "tank solution" in which cadavers may be kept as in the foregoing long formula: Saturated solution, 1 drachm (3.9 Gm.): sodium arsenate, 6 Kg.; potassium nitrate, 4 Kg., and fontana, 40,000 cc. boiling spring water (10 gallons). "No. 15" solution: borax, 1,500 cc.; boracic acid, 1,200 cc.; potassium nitrate, 3,000 cc.; boiling spring water, 57,000 cc.; thymol, 30 cc.; acid salicylate, 180 cc.; alcohol (95 per cent), 1,800 cc.; formaldehyde solution, 1,800 cc., and oil of eucalyptus and oil of lavender, 32 minims (2.02 cc.).

These should be prepared as already outlined; take 2 gallons of no. 15 solution; a tank of ½ gallon, and ½ gallon of saturated solution; dissolve the phenol in the tank solution and then add the no. 15 solution and the saturated solution. I believe that the phenol can be left out and the solution will remain clear.

Specimens.—The first specimen, from 1910, was from a patient with mental disease, who imagined herself a pincushion; three needles were removed from her nose and seven hairpins from various places in the abdomen; three hairpins were encysted inside the small intestine and two needles had traversed the atlo-occipital ligament and perforated the spinal cord; they were separated from the ventral margin of the foramen magnum of the occipital bone and were not the cause of death. The patient had been in the habit of secreting herself under her bed after having found a hairpin. She would then push the hairpin into the umbilicus and press the abdominal wall against the floor until the hairpin had disappeared. She died of peritonitis and a huge abscess in the right rectus abdominis muscle.

The brain was kept in the first solution and was changed to the solution last mentioned. It is in good condition, although it has been handled at least once or twice a year since 1914.

The other brains have been in the solution, one for ten years, one for one month and the other for one week.

In the cadavers, which are usually secured from four to six or seven days after death, certain decompositions have taken place; blood forced out of the veins is black, gradually clearing to an arterial red.

The solution should be neutral, rather slightly alkaline, but never acid. This fact was pointed out by William Hewson, F.R.S., in 1766. I did not know of

this, except from my own experience, until attention was called to it by looking over his work in the Royal College of Surgeons in London, in 1925.

DISCUSSION

DR. JOHN A. KOLMER: Are the colors preserved in diffuse sunlight? Is it necessary to keep the specimens in a dark place? Does the fluid preserve the tissues for histologic examination? I wish a fluid could be devised, that would be capable of injection into the arteries before an autopsy and would preserve the tissues without harm to histologic examination. If this were possible, one would have less trouble with undertakers who are prone to discourage autopsies.

DR. A. HEWSON: It is possible to use this solution and put the part directly in the sun. No histologic studies have been made after the use of the preserving fluid.

THE PLACE OF NEUROSURGERY IN THE TREATMENT FOR EPILEPSY. DR. WILDER PENFIELD, Montreal.

A discriminating attitude must be taken in regard to epilepsy; all therapy must be based on a logical hypothesis that bears the inspection of pathologic studies and physiologic considerations. The empiric method in treating this disease has been followed too long. Even though medicine has failed to cure the majority of patients with epilepsy, as a surgeon has recently pointed out, that is no excuse for an illogical or ill-considered surgical attack on the problem. It is not enough for a surgeon to remove sympathetic nerves that go to the brain simply because they are there, without a guiding hypothesis. It is not enough to open cysts which are on the surface of the brain and which in reality are benign collections of fluid "ex vacuo," or to paint such cysts with corrosive fluid. It is not enough to do a suboccipital decompression without a guiding hypothesis, nor to remove a cortical motor center merely because limbs which are partly under the control of those centers are involved in the attacks.

Epileptic seizures must be considered to be phenomena of positive stimulation. Curiously enough, Hughlings-Jackson has been quoted as sponsoring the view that epilepsy is an escape phenomenon. On the contrary, he pointed out in 1875, in a report from the West Riding Lunatic Asylum, that two phenomena are involved in an epileptic seizure: (1) the positive phase, in which the convulsive seizure is seen, and (2) the paralytic phase. Following the positive phase and during the paralytic stage, mental automatism may appear, due to paralysis in a very high physiologic level, so that there is a release in the lower planes of mental activity.

The treatment for epilepsy by the surgical removal of large portions of the intestinal tract is hardly on a firm foundation. The treatment for the intestinal tract, for the present at least, could be better carried out by conservative medical procedures. When a cerebral scar has been caused after an injury to the head, the practice of removing the dura and replacing it with a transplant of fat or fascia, or a layer of fascia or celluloid, cannot logically be expected to improve matters. The transplant or implant is included in a second scar which is possibly even more dense than the former, and the scar in the brain which extends down into the cerebral tissue is unaltered thereby. Excision of motor cortex in cases of jacksonian epilepsy has been carried out by a number of surgeons, but, of course, the lesion may lie at a distance from such a motor area and an irritative focus in the frontal lobe may cause a spread of excitation, which passes backward and gives evidence of its presence when it reaches the motor cortex. The motor cortex, therefore, in such cases may be only a part of the pathway of the excitation, and not the origin of it. The injection of alcohol into the motor cortex also must result, I should think in a very dense scar in that area. The practice of evacuating cysts of the surface of the brain and painting them with iodine brings up the question of the nature of these cysts. It is common in epilepsy to find diffuse atrophy of the brain. There is an enlargement of the ventricles and

with the convolutional atrophy the sulci become much wider; the cerebrospinal fluid lakes, therefore, between the sulci are deeper and wider than normal. These collections of fluid should not be called cysts. It has been pointed out that at autopsy their presence is not evident. This is due to the fact that the cerebrospinal system is opened at some point in the removal of the brain, and the so-called cysts collapse. If they are connected with the general circulation of the cerebrospinal fluid, they should not be expected to cause local irritation by pressure. In cases of long-standing epilepsy, when there is an enlargement of the ventricles and the presence of these collections of fluid on the surface, the pressure of the cerebrospinal fluid by lumbar puncture, from my experience, is not high but low. If these so-called cysts were a source of obstruction, one would expect the pressure to be high, and in that case the enlargement of the ventricles should be considered due to obstructive hydrocephalus. The cause of the enlargement of these spaces of fluid is better explained by the theory that with each attack there is a certain amount of cerebral destruction, and Spielmeyer has pointed out that there are focal perivascular areas of necrosis in such cases.

It has been urged that suboccipital decompression, in order to enlarge the outlet of the venous sinuses, will decrease the pressure of the spinal fluid in cases of epilepsy, and it has been assumed that the mechanism for the production of these attacks is that the exit for venous blood into the jugular vein is too small and causes a blocking back of blood and an increase of intracranial pressure. There are two arguments against this theory. First, lumbar or ventricular puncture does not show an increase of pressure in the spinal fluid in these cases. Second, when a tumor is present in the posterior fossa, which certainly causes an increase of the cerebrospinal fluid pressure and must embarrass the flow of blood through the sinuses in the posterior fossa, epilepsy is exceedingly rare.

McClintock has recently reported the removal of the superior sympathetic ganglion, combined with the injection of alcohol into the sheath of the carotid, in a large number of cases. The cases were taken without selection and all were done before there was an opportunity to study the result in any. Nevertheless, he is working in an interesting field. The procedure is not new, as it was employed years ago and given up. Four years ago, in a case of mine which showed obvious sympathetic involvement at the time of the attacks, a case of the type of cerebral change which has been called endarteritis calcificans cerebri, complete removal of all the sympathetic nerves to one side of the brain converted generalized epilepsy into unilateral epilepsy, the convulsions occurring only in the side opposite the hemisphere on which operation was not performed. However, in another case of long-standing epileptic seizures, although there were many sympathetic phenomena, complete removal of both superior sympathetic ganglia, decortication of both carotid arteries, removal of all the vertebral nerves and decortication of both vertebral arteries failed to abolish the convulsions. Therefore, it would seem that epileptic seizures are possible in the absence of any sympathetic nerve fibers passing into the cranial cavity.

Nearly all of the cranial nerves give fibers to the plexus of nerve fibers in the pia. The question arises as to what part they may play in the control of pial vessels. It seems obvious that vasomotor changes play at least some rôle in the production of each case of epilepsy. The changes reported by Spielmeyer in the brain, which point to a functional obliteration of small arteries during an attack, and much other evidence, which will not be summarized here, indicate that vascular contraction is possible.

With the brain exposed, during an attack when there was very little respiratory embarrassment, I have seen the arteries gradually become blue and the veins collapse. At the close of the attack the arteries pulsated vigorously. This might suggest that the vascular bed, between artery and vein, had been shut off during the attack. Again, following an epileptic seizure which was induced on the operating table with the cerebrum exposed, there appeared six or seven punctate areas of anemia, each area being 3 or 4 mm. in diameter and each situated at

the apex of a convolution. These areas gradually faded in five or ten minutes. These areas, which lay largely in the motor area, seem to have been produced by focal vascular contraction. This might well be a cause for the gradual appearance of cerebral atrophy.

In the treatment for posttraumatic epilepsy, due to injury at birth or to direct injury of the head in adults, it is more rational to remove the cerebral cicatrix completely if it is localized and not part of a diffuse process. Such a removal results in a fluid filled space, whereas any procedure short of that leaves a contracting cicatrix which is capable of pulling on the rest of the brain and which, in addition, contains a very rich plexus of vessels that may of itself be an etiologic factor in the production of jacksonian epilepsy. In the study of these cases it is necessary to take into consideration the various cortical fields outside the motor area, which enable one to localize the origin of the excitation. This should be followed by encephalography which, in the case of a contracting scar, will show deviation of the ventricles toward the lesion. Finally, operation should be performed under local anesthesia, and electric exploration of the cerebral hemisphere should be carried out. If stimulation of a suspected lesion reproduced a convulsion which is typical for that patient, radical excision of the lesion is justified.

DISCUSSION

Dr. William G. Spiller: Foerster has said that in the epileptic attack pallor of the cortex of the brain is the initial stage of the attack, and that even in jacksonian epilepsy the pallor may begin in the center corresponding to the portion of the body first affected in the convulsive seizure. This is the result of vascular spasm and supports Spielmeyer's theory of vascular spasm as the cause of alteration of the cortical nerve cells in epilepsy. It seems to give a basis for the use of sympathectomy of the superior cervical ganglion in the treatment for epilepsy, first recommended by Alexander, Chipault and Jonnesco, but Dr. Penfield states that he has never seen this pallor, even while operating with Foerster. I was working in the laboratory of Dejerine at the Salpêtrière in 1895 when sympathectomy in epilepsy was first discussed, and I recall the disfavor with which he regarded it. The method fell into disuse, possibly because the persisting effect, as shown by Foerster, is vasoconstriction. Dr. Penfield reported one case in which unilateral sympathectomy of the brain caused a cessation of convulsions, but he immediately reported another case in which complete bilateral sympathectomy failed to stop the attacks. Operation on the inferior cervical ganglion is not without danger.

In epileptic persons, faradic irritation from any part of the cerebral cortex may produce convulsions, even in focal epilepsy. In watching the surgeon stimulate the cerebral cortex with the electrode, I have felt that the repeated stimulation might yield incorrect results, and that an area which at first did not respond might be placed in a state of hyperexcitation (facilitation).

Dandy has stated that in the dog the motor cortex is the only part from which clonic convulsions may be obtained by electric stimulation, and therefore these convulsions must have their origin here. Sherrington and Leyton removed the motor cortex of each side of the cerebrum in the chimpanzee, and complete restoration of motor function occurred. Later, after the animal had entirely recovered, it was impossible to obtain movement by electric stimulation from any part of the brain. If voluntary movement can be initiated outside the motor cortex, why may not clonic convulsions be produced in a similar manner? Foerster has found that tonic-clonic movements occur in animals with only pons, medulla and spinal cord.

Collier recently expressed the opinion that status epilepticus is an interesting frontal symptom. He had records of two cases of patients who were in the hospital under treatment for fits, in whom no signs of a local lesion of the nervous system were observed. Status epilepticus developed in these patients,

and they died; in both cases a frontal tumor was found. He had no knowledge of any other region of the brain in which a tumor produced status epilepticus. Recently, a patient in my service had status epilepticus involving chiefly one side. Death resulted, and an area of scar tissue from a previous thrombosis was found posterior but close to the intraparietal fissure.

Excision of the motor cortex was performed by Horsley and has been supported by Bergmann and others. Possibly merely removing the pia might suffice, as this would impair the blood supply of the part but cause less destruction than removal of the cortex. The pial vessels have nerve fibers. Such fibers were demonstrated by Obersteiner many years ago, and more recently by Hassin.

Dr. Penfield has described in detail the removal of cortical scar tissue. The longest period after this operation mentioned by him was three years. This is sufficient time to afford a favorable indication of benefit, but more experience will be needed. We must know whether the surgical damage of the brain is unattended by serious consequences.

I should like to know Dr. Penfield's attitude toward operation in jacksonian epilepsy. In some cases I have seen brilliant success from operation, but in other cases, no less typical clinically, no lesion has been found. It is desirable to do the operation when the lesion is small, but this means that in some instances no lesion will be found if an operation is performed before symptoms have become pronounced.

DR. CHARLES H. FRAZIER: I always anticipate with pleasure hearing Dr. Penfield speak. His remarks are always based on substantial evidences, usually the result of his personal observations. In thinking of what I might say in discussing his paper, I thought that I might relate my experience in the treatment for traumatic epilepsy. From the surgical point of view it is essential to know the character of the lesion with which one has to deal. From a summary of 105 cases of traumatic epilepsy in my records, I found that the lesions fell into 5 groups: (1) The major lesion involved the membranes, a thickening of the arachnoid or dura, with or without adhesions—an arachnitis or pachymeningitis. There were 30 of these. (2) In 9 cases the lesion was essentially vascular; there were tortuosity and dilatation of the cortical veins; in 2 cases there were true hemangiomas. (3) In 34 cases there were cranial defects of considerable dimensions. (4) In almost a third of the cases there was what once was called pathologic edema, when it was not realized, as it is now, that the basic lesion is shrinkage of the brain and the excessive fluid in the subarachnoid space merely takes the place of the reduction in brain volume. (5) In only 10 of the series were the observations reported as negative, although the surgeon is conscious of the fact that while the naked-eye appearance of the cortex may be normal, in these cases there may be some structural changes in the cortex itself.

In considering the pathologic lesions as depicted in the encephalogram, it was surprising to find that among the 140 encephalograms from the neurosurgical clinic, the deviations from normal in the cases of traumatic epilepsy corresponded almost exactly with those of patients who have come under observation suffering from the late effects of cerebral trauma, headaches, tinnitus and vertigo. The encephalographic picture of the general enlargement of the cerebrospinal fluid pathways, a pocket of air over one or both frontal lobes and a dilatation of one or both ventricles is so constant that in the future one may question the propriety of subjecting a patient to the discomforts incidental to the injection of air.

Considering the surgical aspects of the various pathologic lesions, as already described, obviously the cases with excessive fluid in the subarachnoid space present no indication for operative relief. It must be remembered that in most instances, even with this seemingly diffuse lesion, the seizures were focal in character, as in the daughter of a physician who was operated on the other day. The attacks were of such a character that there was reasonable ground for suspecting a neoplasm. On the other hand, I have always maintained that the

large cranial defects furnished positive indications for surgical intervention. Remembering that the membranes are usually adherent to the margins of the defect and to the scalp, if one believes at all in the harmful influence of cortical irritation and of traction on the cortex, as affected by posture and atmospheric conditions, one can assume the propriety of a conventional plastic operation, a cranioplasty. I performed this operation many times in the reconstruction period after the World War, and only today had occasion to review the record of one of this series, in which the result has been satisfactory.

Whether one should interfere at all with the vascular lesions is a debatable question. The possibility of paralysis or other disturbances of function following ligation is not imaginary. In one case of my series the patient developed a spastic hemiparesis which has persisted for many years.

Dr. Penfield has told us what might be accomplished by extensive resection of damaged sections of the brain and in this he has made a definite contribution. He has opened a vista of hopefulness in a field that was otherwise regarded as without promise. One fourth of our series might have been treated by the Penfield method.

It was at Dr. Grant's suggestion that I resected the first and second thoracic sympathetic ganglia, on the hypothesis that there is a vasoconstriction of the cortical vessels preceding the seizures. I was especially interested, therefore, in hearing Dr. Penfield's experience with the sympathetic approach to this problem.

I abandoned long since Horsley's practice of excision of a cortical center, nor was I ever impressed with the idea of subtemporal decompression as proposed by Kocher many years ago, on the grounds that the attacks are preceded by a transitory increase of intracranial pressure.

As Dr. Penfield says, there is no panacea for the treatment for epilepsy. Certainly surgery offers none, and yet one cannot ignore the favorable results that have followed surgical intervention in some cases. Referring to a paper published in 1912 (Frazier: Personal Observations and Deductions as to the Pathogenesis and Surgical Treatment of Epilepsy, Based Upon a Series of Sixty-Three Cases, *Therap. Gaz.*, March, 1912), I find that of twenty-five cases, seven were favorably influenced by operation. In one, the attacks were less frequent and less severe, occurring once in two months; in one, there had been no attacks in three years; in one, gradual subsidence of attacks, with none for the past nine months; in another, only one attack since operation and none for the past three and one-half years; in another, no attacks since operation, and in the remainder of the seven cases only one mild attack in four years.

DR. TEMPLE FAY: Dr. Penfield's paper is interesting, especially in regard to focal epilepsy. He has demonstrated three cases in which removal of scars from the brain was followed by relief from seizures. When the entire group of epileptic patients is considered, this type of lesion is comparatively infrequent. During the past five years, the major convulsive seizures in all types have been controlled by proper fluid balance and dehydration. Cases of organic lesion, such as those which Dr. Penfield has shown, have become focal jacksonian in type after the relief from the major seizure. Scars of the brain in themselves are probably not responsible for convulsive seizures. The situation of the scar is far more important than the lesion itself. It is evident that the scar does not produce the seizure for two reasons: If its irritation were sufficient there should be continuous convulsive manifestations, and if the scar produced destruction there would be paralysis.

Dr. Penfield has not mentioned the important significance which such a scar situated in the frontoparietal region may have in relation to cerebrospinal fluid circulation and variable pressure produced by obstruction of important fluid pathways. Certainly the intermittent occurrence of convulsive seizures indicates that the factor responsible for predisposing the patient to a convulsion at one moment is absent during the period when he is free from attacks. This predisposing

factor has been shown clearly to be due to a disturbance of water metabolism and a storage of fluid, with resultant increase in the volume and pressure of cerebrospinal fluid.

Dr. Penfield points out the atrophy described by Spielmeyer, Winkelman and others, without indicating its cause or its origin. The distribution of this atrophy indicates that it lies within the circulatory field of the cerebrospinal fluid. We have offered fairly definite proof in a series of papers that this atrophy is due probably to hydraulic pressure exerted on the cortex in the fluid field. In assuming that this atrophy of the brain precedes the increased collection of subarachnoid fluid, permitting additional space which the fluid fills, I should like to ask Dr. Penfield if the mechanism of internal hydrocephalus due to obstruction of the acqueduct of Sylvius or a lesion of the posterior fossa can be considered in this light. Certainly the atrophy produced by the dilatation of a ventricle is well recognized to be secondary to pressure, and one would not say that the atrophy occurred from some unknown cause and that the fluid within the ventricles merely filled the dilated spaces. The atrophy of the brain found over the cortex is in all probability due to the same cause as the atrophy seen in internal hydrocephalus with marked dilatation of the ventricles, the only difference being that one now recognizes that a definite form of obstruction is found at the point of outlet at the vertex, as Winkelman has clearly shown, and that this obstruction is capable of producing an overaccumulation of fluid in external hydrocephalus in the same way that gross obstruction in the posterior fossa produces the internal type.

In conclusion I ask again why Dr. Penfield believes that a vasomotor impulse or response is necessarily responsible for the convulsive seizure. In stimulation of the vessels such as he describes there is no assurance that the faradic irritation may not produce the central response through the fibers on the vessels, as well as the peripheral response, focal in character. Vasomotor responses confined to one branch of the middle cerebral artery might be expected to disturb the physiology of the focal area, but certainly a generalized convulsion implies that the stimulus has spread beyond the vascular supply of one branch and even to the opposite hemisphere. This is possible only through a central reflex response. Irrespective of the points involved in the focal origin of attacks, the question remains as to why the patient is free during certain intervals and becomes a victim of a seizure only at certain times. There must be a variable factor outside of the focal lesion and the vasomotor system, and this variable has been clearly shown to be concerned with the metabolism of water.

Dr. Penfield has made an outstanding contribution in his studies of the formation of scars in the brain and surgical methods for their prevention, but even with the excellent results that he is able to obtain, I believe that neurosurgery offers little from the operative standpoint in the solution of the problem of epilepsy other than in cases that show definite signs of an organic lesion or encephalographic evidence of gross scars such as he has described.

DR. N. W. WINKELMAN: Is Dr. Penfield in total agreement with Spielmeyer and others that the changes in the brain in epilepsy are the result of angiospasm? I ask this in view of my personal observation of the same sort of pathologic picture in the case of temporary anoxemia in a patient who stopped breathing for about five minutes during an operation. In this case, however, there was a marked swelling of the lining cells of the small vessels. I have felt that the changes that occur in epilepsy might likewise be the result of the same sort of process from the temporary anoxemia that occurs at each epileptic convulsion.

DR. WILDER PENFIELD: It is easy to see that statements must be backed with excellent evidence before they go unchallenged in the Philadelphia Neurological Society. Dr. Winkelman spoke of differing with Dr. Spielmeyer with regard to functional obliteration of small vessels. I assume that Dr. Winkelman believes that Spielmeyer merely failed to find the objective evidence of block, although that evidence was there to be found. The difference seems to be a

matter of pathologic technic and critical interpretation which I am in no position to discuss. Dr. Spielmeyer would be willing to agree that in many cases there is a true organic obstruction, but he maintains that in other cases there must have been merely a temporary, functional closing of the vessels.

I did not understand Dr. Fay's question in regard to the obstruction of the aqueduct of Sylvius. I did not realize that there was any such obstruction in cases of epilepsy. A block in the aqueduct of Sylvius would cause obstruction, of course, but arachnoid cysts in cases that do not show a general increase of spinal fluid pressure and that collapse when the cerebrospinal fluid is withdrawn can hardly be called obstructive; in my opinion the patient should not be considered to be in need of dehydration merely because such cysts exist.

With regard to the relationship of trauma to secondary epilepsy, I think that the best evidence is that of Wagstaffe, who analyzed seven hundred cases of his own after the war. He found, in dividing up injuries of the head into those in which the dura was penetrated and those in which the dura was not penetrated, that epilepsy occurred in 19 per cent of the former and in only 1.6 per cent of the latter. I think that if his examination could be conducted ten or fifteen years later (which is impossible, as Dr. Wagstaffe has recently died) there would be a higher percentage of epilepsy in cases with depressed fracture.

Dr. Frazier's long series of cases illustrates the fact that in his presence I am a newcomer in neurologic surgery. In regard to cranial defects, I should agree with Dr. Frazier that it may be wise to close the defects; when there is epilepsy, however, one should not stop at that, but should at the same time excise all of the cicatricial tissue that lies beneath. In regard to the cessation of attacks after encephalography, I have noted a general decrease in attacks, and sometimes there is complete cessation for a period. In looking over thirty recent cases in which encephalography was carried out but not followed by operation, I find that only two patients were made worse and these not remarkably so. One patient was relieved entirely for six months; many were slightly improved. However, in my opinion encephalography is not to be used as a therapeutic procedure alone. I should point out that if the stellate ganglion is excised without touching the other portions of the cervical sympathetic, axon reflexes are still possible through the superior sympathetic ganglia; it may be that such axon reflexes are important in the production of certain seizures.

I invariably find Dr. Spiller's questions embarrassing because they are much too searching. Certainly, electric stimulation of the cerebral cortex is not so simple a procedure as the outline of motor areas would lead one to believe. I have never been able to map out in a human case all of the motor areas that appear in textbooks. Sherrington and his co-workers have shown by stimulation of the cortex of the ape that if you produce a movement of a certain limb by cortical stimulation you can reproduce that movement by stimulation of the cortex at a distance. Thus "by facilitation" the same movement can be produced from various areas. It should be remembered also that the Betz cell areas are deep in the fissure in some places and are not present on the surface. Radical cortical excision should be carried out only when one can produce an attack by faradic stimulation of the suspected area. The small dose of galvanic stimulus used to outline motor areas is not sufficient to produce an attack. Very strong stimuli may produce movement in almost any area. I do not advise the removal of motor areas in the absence of a frank cicatrix merely because it is possible to produce a convulsion from that motor area. Of course, that might be possible in any normal case.

Vertebral fibers, or the sympathetic nerve on the vertebral artery, can be removed without touching the stellate ganglion. The size of the so-called vertebral nerve is, in some cases in human beings, as great as that of the vagus. Therefore, it is wrong to assume that the removal of a superior sympathetic ganglion removes all the sympathetic fibers going to the vessels of the brain.

Dr. Adson, who is speaking here next week, will make you believe, no doubt, that it is the "summum bonum" of life to have sympathetic ganglia removed. He can answer Dr. Spiller's fear as to the result of the removal of these ganglia better than I.

In regard to the question as to what patients with epilepsy should be considered proper subjects for operation, it seems to me that every case of focal epilepsy should be looked on with suspicion. This would include cases in which the convulsive pattern is always the same and is characterized by a turning of the head and eyes in the same direction, by a definite sensory aura or by some other phenomenon which suggests that the stimulation arises in a focal area. This enlarges somewhat the conception of jacksonian epilepsy.

With regard to Dr. Spiller's question as to the meaning of the word "adversive," I had supposed that it referred to the fact that the adversive fields lie next to the motor areas, but I do not know who first used the term.

In regard to the subsequent scar after radical removal of a cerebral cicatrix, I have no hesitancy in answering because of six years intermittent research on this question. A clean removal of cerebral tissue or scar does not give the same result as a gross injury to the brain. If cerebral tissue is injured and left in situ, a contracting cicatrix is formed which contains connective tissue and new-formed blood vessels. Clean excision of cerebral tissue does not result in such formation but in the appearance of a fluid-filled space. The question of greatest interest to me just now is whether or not the new-formed vessels in the scars bear vasomotor nerves.

The end-results, for which Dr. Spiller asked, I am unable to give him. The series to which I referred recently in New York consisted of cases of Dr. Foerster. He is completing the follow-up in these cases; it is eighteen months since I worked on the subject with him in Breslau. At that time the oldest of the cases were about five years after the radical removal of the cerebral scar. These results will be published. I can give as my impression only that certainly one half of the patients operated on have been completely free from convulsions for periods up to five years. Of the patients whose cases I reported, each has been free from an attack since radical excision. In one case the duration since operation is only six months; in another, it is eighteen months, and in a third, a little over two years. I realize that this time is too short to permit any definite conclusion. One must wait a lifetime before drawing final conclusions with regard to any method of treating epilepsy. What I attempted to do was to point out the necessity of finding a rational basis for attack on this disease rather than to follow the "wandering fires" of empiricism.

Book Reviews

GRUNDELEGENDE UNTERSUCHUNGEN FÜR DIE ANGIOARCHITEKTONIK DES MENSCHLICHEN GEHIRNS. By DR. RICHARD ARWED PFEIFER. Price, 37.6 marks. Pp. 220, with 187 illustrations and 2 tables. Berlin: Julius Springer, 1930.

This beautifully illustrated book gives an account of the vascular patterns found by complete capillary injection of the human brain. Many problems in cerebral circulation that have long been under discussion receive an apparently final answer. The arteries of the brain show a form perhaps to be ascribed to the effect of hydrodynamic forces. As a result of giving off branches under high pressure, the larger vessels pursue a slightly zig-zag or corkscrew course. Branches are given off usually at almost right angles to the main stream, finally ending in terminal arborizations with widely spread limbs. There is a slight conical enlargement at the base of each branch, and the main trunk is slightly narrowed beyond. The old conception of cortical arteries and medullary arteries distinct from one another is incorrect; the vessels running in from the pia supply both gray and white matter. There is a rich anastomosis throughout the arterial system, in both small and large vessels. The veins are much more numerous than the arteries. They appear smaller in injected specimens. Tributaries join the main trunks in characteristic graceful curve — "fleur-de-lys" or "sea-anemone" forms. Groups of "cascade" veins are seen to empty into large sinuses. As in the case of the arteries, long veins receive tributaries from both white and gray matter. The veins of the hippocampus are particularly large.

Cohnheim's theory that the vessels of the brain do not anastomose must be abandoned. Not only are there anastomoses between main arteries, in the capillary net and among large veins, but vessels bridge the ventricles and extend from one convolution to another and from the dorsal to the ventral side of the brain stem. The mechanism of infarction must include other factors besides the normal arterial pattern. The vascular system of the cerebral white matter is arranged in beds which follow the course of the fibers to a certain extent but in general preserve their own orientation perpendicular to the ventricles. These vascular beds are as distinct in their architecture as those of the cortex. The arteries are twisted and knotted; the small veins are short and straight, as if to equalize the flow of blood. Definite arteriovenous anastomoses are described and illustrated. Some veins, therefore, contain mixed arterial and venous blood. The author attributes a suction effect to this arrangement.

Illustrations are given of certain cortical fields, both in injected specimens and in cellular stains, for comparison. Although the vascular architecture is fairly characteristic for different cortical fields, it does not always correspond with the cellular architecture. Vascularity appears to be greatest in the areas rich in protoplasmic nerve cells.

The dura possesses an outer and an inner vascular network. The former anastomoses with the diploë; the latter with the meningeal vessels. There is also a complicated "lymph" system.

The cerebellum is supplied from its outer surface by festoon-like and comb-like pial arteries extending into the fissures where they give off many short branches. All of the main arteries anastomose freely with each other, as do also the veins. Many vessels pass directly through a convolution to join the trunk on the opposite side. The Purkinje-cell rete is by no means unique; vascular nets often occur between cortical layers in the cerebrum also. The nucleus dentatus has an extremely rich blood supply.

Around many of the medium and larger sized vessels of the brain a definite circumvasal capillary-free area may be demonstrated. It is bridged by smaller connecting vessels and also by recurrent vessels to the vasa vasorum. It is much

larger than the confines of the spaces of Robin and His. The author does not point out the extreme importance of this fact in relation to demyelinating processes which have such a definite predilection for the vicinity of vessels. If vascular rupture into one of these perivasal spaces occurs during injection (and presumably also in vivo), the extravated mass follows the vessel along as a sleeve or cone. The author suggests that this is one mechanism by which small hemorrhages are kept from spreading widely.

This book should be in the hands of every neuro-anatomist and neuropathologist. It marks a great advance over the author's previous monograph (Die Angio-architektonik der Grosshirnrinde), in the first place because it describes the human brain, in the second place because it is more complete and rounded and in the third place because the priceless anatomic data are somewhat less diluted with vague philosophic intimations. One could wish still that the author had shared with us some of the secrets of his injection technic (not even the materials used are mentioned) and that less space were devoted to criticism and illustration of the older workers in the field with whom he disagrees. However, we are none the less under a great debt to him.

L'ÉPILEPSIE; CONCEPTIONS ACTUELLES SUR SA PATHOGÉNIE ET SON TRAITEMENT. By P. PAGNIEZ. Price, 26 francs. Pp. 192. Paris: Masson & Cie, 1929.

The author is concerned mostly with "essential" or cryptogenic epilepsy. There are two factors to be considered: one the nervous, and the other the humoral. The present-day tendency centers the problem of the pathogenesis of epilepsy on the humoral factor. It is with this last factor that the author is principally concerned in this book.

Chapter I is a historical review of the experimental production of convulsions in animals with particular stress laid on the work of French and American authors, pointing out the combined effect of cerebral lesions and of toxic agents as the optimum condition to obtain experimental epilepsy. In chapter II the author points out the nonspecific character of lesions found post mortem from the standpoint of both their nature and their localization. The cerebral lesion is, however, an important though not absolute factor in the pathogenesis of epilepsy. The infections of the central nervous system are probably the most common source of such lesions. It is the scar formation that seems to play a particularly potent rôle in subsequent convulsions. Chapter III deals with the metabolism of nitrogen, cholesterol, carbohydrates, etc. The author is not critical of the work reviewed. In general, the metabolic studies did not yield definite data as to the existence of specific or characteristic anomalies in the metabolism of epileptic patients. The author's greatest interest lies in his theory that an analogy exists between epileptic attacks and anaphylactic shock. There are cases in which this analogy is so close as to allow one to speak of the identity of paroxysms of both types, but such cases are rather exceptional; on the other hand, there are many arguments opposing the anaphylactic theory of epilepsy. This chapter is made particularly interesting because of the personal contribution of the author to its topic. The same has to be said about chapter VI as there exist at certain moments toxic substances in humors of epileptic patients. These substances have a distinct convulsion-producing effect on experimental animals. The nature of these products is unknown; possibly their effect is induced through the vasomotor disturbances as suggested by the observation of B. Meyer on the excised arteries of the calf.

In chapter VII the endocrines play their part in the pathogenesis of epilepsy; however, the results of numerous researches in this field are not of the kind to permit one to draw any definite conclusion. The endocrines can influence the onset and the evolution of epilepsy; notwithstanding this, they do not play an exclusive rôle. Epilepsy is not an endocrinal disease. The rôle of the neurovegetative system in the pathogenesis of epilepsy is subordinated to the humoral and glandular disturbances. Nothing so far permits one to look on epilepsy as a direct result of the primary disease of the neurovegetative system in the sense of an essential

vagosympathetic dystonia. The chapter on therapeutics is the longest and gives a very complete and well up-to-date review of the methods of the treatment for epilepsy; dietary treatment and medical treatment are discussed in separate paragraphs. The observations on the effect of different methods as shown in clinical metabolic and biophysical changes in patients (fasting, ketogenic diet, artificially induced acidosis, protein therapy, phenobarbital, phenylmethylmalonylurea, potassium borotartrate, etc.) are considered from the standpoint of their bearing on the problem of pathogenesis. The book is closed with a summary of modern conceptions of the pathogenesis of epilepsy. The main acquisition of present-day research is that in the mechanism of epileptic accidents an important and probably predominant part belongs to the humoral factor. The thoughtful and careful manner in which the author treated his complex subject deserves much praise.

MEDIZINISCHE ANTROPOLOGIE. EINE WISSENSCHAFTSTHEORETISCHE GRUNDLEGUNG DER MEDIZIN. By DR. OSWALD SCHWARZ. Price, 13 marks. Pp. 383. Leipzig: S. Hirzel, 1929.

The author and editor of "Psychogenese und Psychotherapie körperlicher Symptome" gives a philosophical discussion of the position of medicine in the system of human fundamental attitudes, a disposition or outline of a system of medical anthropology including: (1) Man as part of nature (in four layers — the nonvital, the vital, the psychic and the mental). (2) Man as the creator of culture viewed as action, in the form of sport, dance, drama and language as levels of objectivation, followed by a discussion of a general schema of production seen in experiences, creation and understanding. The activation of this understanding illustrated by the psychologic system — psychoanalysis, individual psychology, the Dilthey-Spranger type of psychology and the pathology of production. (3) Man as a member of the community.

After a division on the position of this anthropology in a system of the sciences, he reviews as the basic concepts of medical anthropology the type, the norm and the sick, and as basic concepts of medicine its position among the forms of human activity, disease (concept and nature, symptom and diagnosis) and therapy. Finally he reviews the philosophical trends in present-day medicine. The work belongs to that philosophical discussion peculiar to present-day German and Austrian, especially neuropsychiatric flight into abstraction. Although definitely labored, the trend marks the maintenance of an intellectual culture that has to be understood with an evaluation of several of the prominent medical-philosophical leaders. To Anglo-Saxon thought the whole movement looks like a product of "hypertension," of surfeit of struggle with detail of abstraction, and the unrelenting desire to create and recognize systems. Where we might say that we reach out for order in simplicity, we meet here a flight into complexity which is part of a cult of philosophy not unlike the phase of one hundred years ago. Will it help or burden the growing generation? Probably both. Nothing short of a genius will ever bring together what philosophical thinking connects Anglo-American medicine and these ultra-serious preoccupations. If there is any transference of endurance and discipline from the flights into this philosophy to creative experimental activity, the labor will be worth while; otherwise, this modern edition of "Naturphilosophie" will become a dangerously autistic cult of the few and of struggling followers. The book is well written, but discursive and more a discussion for the initiated than for the seeker of orientation. The final chapter and the bibliography are a notable exception to this general statement.

This quest for a basic science underlying all the special sciences dealing with the "world," the "logos of nature," forms indeed a remarkable contrast to Dewey's discussion of the "Quest for Certainty." The author calls his book "a confession of that noble idealism for which that which is individual is of value only to the extent to which it attains significance for the general."

Any one who would wish to write an Anglo-American counterpart of a medical anthropology will find this work a stimulating expression from another world, akin to ours in the effort to apply methodical accuracy to the conviction of continuity from the simplest biologic function to the highest mental attainments.

CLINICAL STUDIES ON EPIDEMIC ENCEPHALITIS. By G. BERMANN. Pp. 226, with 15 figures. Córdoba: Lutz Ferrando & Cia, 1929.

The author has brought together in this book his personal observations in many cases of epidemic encephalitis in Argentina, which he discusses in the light of recent progress on the knowledge of this disease. The first chapter is devoted to a study of the occurrence of the disease in Argentina. Since the epidemics of 1919, 1920 and 1921, hundreds of cases have sporadically appeared in diverse provinces and, as in other countries, in many instances the possibility of direct contagion had to be excluded. In Argentina there has never been a focus from which the disease has spread. The latter is more prevalent during the winter months (from May to August in the southern hemisphere), the highest number of cases occurring in June and July. The disease attacked chiefly subjects from 10 to 40 years of age. A discussion of the bacteriology of the disease ends this chapter.

In the second chapter Bermann describes the symptoms, clinical forms, evolution and differential diagnosis of the acute form of the disease, illustrated with case histories. In spite of the polymorphism that has been attributed to epidemic encephalitis, the author believes that the "triad" of von Economo (somnolence, paralysis of the ocular muscles and an infectious state) is still an excellent guide to its diagnosis in the acute stage. In Argentina the predominating form has been the oculolethargic from the beginning, but other forms have occurred, though in small numbers. The physiopathogenesis of epidemic encephalitis is ably discussed at the end of this chapter.

The third chapter deals with the chronic states of the disease, more especially with the postencephalitic parkinsonian symptoms. In order to make clear the nature of these symptoms the pyramidal and extrapyramidal syndromes are compared and discussed.

In the fourth chapter the author reviews the new contributions on the psychopathology of the chronic form of the disease, and agrees in the main with the opinions of Camus and Roussy and Van Bogaert on the existence of a true psychiatry of the mesencephalic region.

The fifth chapter deals with the several aspects of the postencephalitic mental symptoms. The bradyphrenic form of dementia, the syndromes of affective depression in postencephalitic patients in whom no acute form was either detected or correctly diagnosed, the perversions of character and behavior, alterations of speech, spasmodic superogyric crises, cataplegia, endocrine disturbances and tachypnea are illustrated and discussed. The occurrence of considerable numbers of chronic forms of the disease, manifested in the symptoms mentioned, is in contrast with the few acute cases reported. This is due partly to the attenuated virulence of the infection and partly to faulty diagnosis in acute cases.

The book ends with a chapter on the prognosis and treatment of epidemic encephalitis. In the opinion of the author, complete recovery is rare and treatment must be intensive and prolonged during the acute and subacute periods, and even during the chronic phase. A neuropsychiatric study of the disease is advocated.

A list of publications on epidemic encephalitis in Argentina is appended.

LEHRBUCH DER GEISTESKRANKHEITEN. By OSWALD BUMKE. Third edition. Price, 29.80 marks. Pp. 806, with 160 illustrations. Munich: J. F. Bergmann, 1929.

Bumke's text, originally limited to a book on diagnosis, represents today the author's confession of faith and probably that of many German workers. It reviews

the causes and the general symptomatology (perceptions, memory, thinking, emotions, intelligence, consciousness, volition, action and speech), and then the treatment and the medicolegal aspects. The special part begins with the psychopathic dispositions, reactions and developments, the nervous (psychasthenic) constitutions; the psychogenic reactions and the hysterical disposition and other psychopathic constitutions and the treatment. There follow the affective disorders and the manic-depressive constitution, the paranoic dispositions and developments, the organic (heteronomic) reactions and psychoses, symptomatic, toxic, cerebral and syphilitic; then the psychoses of the period of involution and senescence, the epileptic disorders, the schizophrenic disease processes, the oligophrenias and cretinism and myxedema. Excellent and well illustrated outlines of the autopsy data are given by Spatz, and the bibliographic references are given with the successive chapters.

Somewhat less individual than Bleuler's text, but more broadly illustrated, the book represents the practical common sense of the author. Frankly opposed to psychoanalytic dogma and sober concerning psychodynamic formulations that would go far beyond Dubois, the author is fairly free from dogmatism, at any rate on the positive side, but is relatively colorless and definitely closer to the older types of formal psychiatry than to the points of view of most American workers. As editor of the large and expensive Handbuch, Bumke has indeed an unusually comprehensive vision of the practical upshot of the practical and theoretical status of the type now in vogue in Germany.

The book is dedicated to Hoche, who has long maintained a position of independence of Kraepelin's ultranosologic demands. Bumke's conservatism shows in the fact that while only a few years ago he predicted a dissolution of the dementia praecox or schizophrenia entity, he still treats it as a chapter of the organic psychoses, but as having a very good remission after the first attack in 20.9 per cent, fair remission in 18.7 per cent, social adjustment with delusions in 9.3 per cent and a transfer to the "asylum" with a sealed fate in only 18 per cent.

It is not likely that the book would serve American demands to the extent of deserving a translation without adjustments. But it has many features that should command the attention of our readers.

LA FOLIE ET LA GUERRE DE 1914-1918. By A. RODIET and A. FRIBOURG-BLANC. Price, 30 francs. Pp. 194, with 10 illustrations. Paris: Félix Alcan, 1930.

Based on 25,000 observations, the report reviews the manic states, the melancholias, mental confusion and stupor, dementia praecox, essential systematized psychoses, delusions of interpretation and mental automatism, the psychopathic person (developmental and deteriorated), psychoses due to alcoholism, lead, morphine, cocaine, ether and carbon monoxide, autointoxications, infections, exotic diseases, dementia paralytica, cerebral softening, parkinsonism, tabes, epilepsy, hysteria, neurasthenia, simulation, fugues, cyclothymia, hypochondriasis and obsessions.

The authors find that the World War did not produce any psychopathies that had not been known before. On the other hand, the constitutional, habitual and emotional handicaps were definitely brought out by the strains. Jean Lépine found, in 600 cases, more than a third definitely alcoholic psychoses. In the course of time, the depressions increased in frequency. The manic patients were apt to return to the front and to take some time before lack of discipline disqualified them again — masturbation in public, erotic tendencies, exaltation and creation of disorder. The depressed patients were especially apt to show refusal of food and gastro-intestinal disorders, a sense of dishonor and disgust with life; the anxious and many alcoholic patients showed a tendency to suicide and self-mutilation, and the latter also to murder, often in raptus. The confused patients often deserted, as did the psychopathic patients and the patients with dementia praecox, but more through a spirit of opposition, impulse and negativism. The epileptic patients caused much trouble. The patients in cases of simulation often asked to be returned to the front to make good. Patients with delusions tended to turn against officers or companions; they often caused difficulty in court martial.

The practice of disposal had to consider the return to the front of as many patients as possible; others had to be assigned to simpler duty, unless they were actually liable to become dangerous. On the other hand, it was necessary not to increase the number of those who might want to be pensioned later. Assignment to judicious officers and assignment to family care proved very important. On the whole, the authors believe that the showing of moral fiber and sanity was excellent.

The book is hardly to be called a searching survey of the actualities because, obviously, the records during the war were none too complete, and in many hospitals were well nigh suspended.

SOCIAL CONTROL OF THE MENTALLY DEFICIENT. By STANLEY P. DAVIES. Price, $3. Pp. 381. New York: Thomas Y. Crowell Company, 1930.

This book gives a complete and balanced review of the problems presented by the mentally deficient. It covers the subject in a concise, clear and complete way. Davies gives a historical review of concepts regarding the feebleminded. He discusses in a clear and balanced way the point of view of the eugenists, and then various types of work being done in this country in the care of defectives in institutions and colonies, the place of the school, the work that is being done with the defective delinquent and the various activities that are going on within the community for adjusting those of lesser intelligence to the regular life of the community. Here he discusses the place of the school, the work of special classes, vocational adjustments, etc.

He approaches the whole subject from a social point of view. He gives the reader a feeling that problems associated with the feebleminded are live, active problems and that the results obtained through adequate institutional and community supervision fully substantiate the feeling that the care of the feebleminded is much more than just a custodial problem, a feeling that undoubtedly is rather prevalent. If one is not acquainted with the varieties of activities going on in this field, this book will be a revelation.

The book is more than a presentation of a point of view. It is an evaluation of much of the important work that is going on in this country. Attached to each chapter is a short but well selected bibliography. Free reference is made to the literature all through the book. It is well written and can be highly recommended to every one interested in the large problems associated with retarded mentality.

LA MALADIE DE FRIEDREICH. By P. MOLLARET. Price, 50 francs. Pp. 308. Paris: Amédée Le Grand, 1929.

This is a monographic consideration of the disease based on the personal study of twenty-one cases, which apparently have been collected from many of the hospitals in Paris although the work has been done under the aegis of Guillain, Mollaret being his chef de clinique. Although he limits his study to the strictly familial disease originally described by Friedreich, he promises more in a future communication and states that he has come to the conclusion that "there is no sharp boundary separating Friedreich's disease from heredo-ataxia of Pierre Marie."

In Friedreich's disease there are three elementary pathologic traits that may be mixed in various proportions: (1) the cerebellar disturbances manifested in nystagmus and scanning speech; (2) disease of the posterior columns and roots, producing ataxia, abolition of reflexes and sensory disorders, and (3) indications of pyramidal defect resulting in extensor response with reflexes of medullary automatism. The last is usually a late addition. The symptoms and signs are treated in great detail, and the cases are scattered through the text in a way to emphasize the individual variations. At frequent stopping points the author starts a new paragraph with a question in italics, which serves more or less as a guide in bringing before the reader the topic under discussion. The author confesses himself

at a loss as far as treatment is concerned. A complete bibliography is given, and the table of contents is nearly as good as an index. As a clinical study the work approaches the monumental.

DAS WERDEN DER SITTLICHEN PERSON. WESEN UND ERZIEHUNG DES CHARAKTERS. By RUDOLF ALLERS. Price, $2.25. Pp. 316. St. Louis: B. Herder Book Company, 1929.

Rudolf Allers offers in this "Growth of the Moral Person — The Nature and Education of Character" an interesting rendering and elaboration of Adler's individual psychology in terms of what would be acceptable to Roman Catholicism. He treats of the essence or nature of character and the methods of characterology, the conditions of origin (self-assertion, instinct, will and power, inferiority and compensation, the will and training for community), infantile and childhood characters and difficulties of education, the ideal of character and the efficacy of example, the characterology of the sexes, the later years of childhood, school, puberty and sexual problems, deviates and neurotic characters, insight and self-education.

The book is characteristic of the German spirit of today, written with what would seem to the American an unnecessary severity of style and painstaking thoroughness, and with a strong tendency to abstractness even when perfectly concrete and simple rendering of facts, methods and procedures might be more telling and helpful. There is little effort at casuistic presentation of what could best be rendered that way. One has definitely the impression of the writer in his study rather than that of action in the field, and in discussion with similarly minded thinkers and students, thoughtful of completeness of consideration. From this point of view the book is a valuable integration of old-time and present-time wisdom and formal treatment of pedagogic and moral-social education by a physician who has worked as specialist in a wide field, from physiopathologic chemistry to psychology and psychotherapy and is seriously concerned with an assimilation of it all to a thoughtful Roman Catholic philosophy.

PSYCHIATRIE UND WELTANSCHAUUNG. EIN BEITRAG ZUR KULTUR DER GEGENWART. By W. JACOBI. Price, 7.20 marks. Pp. 91. Berlin: S. Karger, 1929.

W. Jacobi, the head of a State hospital in Thüringen, proves himself one of those rare persons who are capable of blending their active life and leisure in a most delightful manner, and the reader who enjoys the blending of literature, philosophy, religion, science and especially practical and theoretical psychiatry finds here a wealth of material, quotations and personal observations and considerations. It would be as improper to try to condense the ninety pages as it would be to epitomize poetry. A remarkable reader with a versatility of personal reaction and responsiveness to the actualities of psychiatric and general literature, the author writes clearly for the love of sharing what he himself derives from leisure, which we readers of American journalism have lost to a deplorable extent. Lange's "Fate and Crime," the problem of heredity, the relation of constitution and outlook in life, the meaning and working of causality, the modern efforts to understand and describe personality, the acquired characteristics, the meaning of education, ethics, Naturphilosophie and religion are included. The author does justice to what he says in the preface. He takes one with him in his orderly but richly diversified meanderings of reading, thought, work and contemplation. It is a pleasure to see that the art of literary correlation is not killed even by medicine.